

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. _____
)	
TEVA PHARMACEUTICALS USA, INC.,)	
)	
Defendants.)	
_____)	

COMPLAINT

Merck & Co., Inc. (“Merck”) alleges as follows:

1. This is an action by Merck against Teva Pharmaceuticals USA, Inc. (“Teva”) for relief from the judgment entered by mandate of the United States Court of Appeals for the Federal Circuit in *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.* (No. 04-1005) as a result of Teva’s fraud, misrepresentations, or other misconduct. That appellate judgment was a reversal of the judgment entered in *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, (C. A. No. 01-048) (JJF), which was entered in this Court.

2. In the prior litigation, Teva obtained judgment in its favor by withholding one of its own patent applications, which contains statements that contradict Teva’s litigation arguments. Without Teva’s withheld patent application before it, the Federal Circuit accepted Teva’s litigation arguments, which form the core of the Federal Circuit’s opinion holding two claims of a Merck patent invalid. Based upon Teva’s fraud, misrepresentations, or other misconduct, Merck seeks relief from the judgment in the prior litigation under Rule 60(b) of the Federal Rules of Civil Procedure.

THE PARTIES

3. Plaintiff Merck is incorporated under the laws of New Jersey with its principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889.

4. On information and belief, Defendant Teva Pharmaceuticals USA, Inc. (“Teva”) is incorporated under the laws of Delaware, with its principal office at 1090 Horsham Road, North Wales, Pennsylvania.

JURISDICTION AND VENUE

5. This action arises under the patent laws of Title 35 of the United States Code, and Federal Rule of Civil Procedure Rule 60(b). The Court has subject matter jurisdiction based upon Title 28 of the United States Code Sections 1331, 1332, 1338 and 1367.

6. Venue is proper in this Court under Title 28 of the United States Code Sections 1391(c) and 1400(b) because the defendant is incorporated in this judicial district.

STATEMENT OF FACTS

I. Merck’s FOSAMAX® Once-Weekly Tablets

7. In 1995, Merck received approval from the United States Food and Drug Administration (“FDA”) for the first effective treatment of osteoporosis. The active ingredient in Merck’s treatment is a compound called “(4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate,” which is usually simplified to “alendronate sodium” or “alendronate.” Merck’s treatment at that time was a tablet containing the equivalent of 10 mg of the free alendronic acid, which patients were to take orally once per day. Merck commercialized its alendronate sodium tablets under the trademark FOSAMAX®. These tablets are usually referred to as 10 mg FOSAMAX® tablets.

8. In April 1997, Merck gained approval for daily 5 mg FOSAMAX® tablets for the prevention of osteoporosis.

9. In 1996, shortly after Merck launched its 10 mg FOSAMAX® tablets, case reports began to circulate of upper gastrointestinal injuries, including severe esophagitis, associated with the ingestion of daily FOSAMAX® tablets. The case reports raised sufficient concern for Merck to warn prescribing physicians about the potential injuries through a “Dear Doctor” letter in March 1996, and to notify the FDA.

10. Alendronate belongs to a class of drugs called bisphosphonates. The commercial development of oral pamidronate, which is the bisphosphonate structurally closest to alendronate, was discontinued after reports of similar side effects.

11. By the time the prestigious *New England Journal of Medicine* published an article entitled “Esophagitis Associated with the Use of Alendronate” in October 1996, Merck scientists had commenced an introspective review of how the dosing regimen for the drug might be changed. Merck undertook research efforts to understand and address the gastrointestinal side effects that were associated with alendronate. Central to these efforts were experimental studies involving beagles performed by Merck scientists. In these experiments, Merck scientists exposed the gastrointestinal tracts of anesthetized beagles to alendronate in simulated gastric juice, and surprisingly discovered that single doses even at high concentrations were not causing the adverse effects that repetitive dosing caused. Although this animal model was extreme, it gave three Merck physicians, Drs. Anastasia Daifotis, Arthur Santora, and John Yates the insight that a multiple of the daily dose administered weekly might be as well tolerated or even better tolerated than daily dosing.

12. The Merck physicians' insight cut against the great weight of the knowledge in the field because the gastrointestinal side effects associated with bisphosphonates had long been reported to be dose related. Therefore, increasing the oral dose by sevenfold was contrary to medical thinking.

13. In 1997, additional beagle studies were undertaken at Merck that surprisingly confirmed the Merck physicians' idea that sevenfold the daily dose of alendronate could be given once per week without exacerbating the side effects, and perhaps with an even better tolerability profile. On July 22, 1997, Merck filed a patent application for the Merck physicians' invention, which described the beagle studies.

14. On November 30, 1999, United States Patent No. 5,994,329 (the "'329 patent") issued to Anastasia G. Daifotis, Arthur C. Santora II, and John Yates entitled "METHOD FOR INHIBITING BONE RESORPTION." Among other things, the '329 patent discloses and claims methods for the treatment and prevention of osteoporosis while minimizing the occurrence of or potential for adverse gastrointestinal effects by giving sevenfold the daily dose of alendronate sodium once per week. Merck is the owner through assignment of the '329 patent. A copy of the '329 patent is attached as Exhibit A.

15. The beagle studies published in the '329 patent explain Merck's experiments on 42 different beagles that were assigned to various groups, which included a control group, beagles subjected to various dosing regimens with three different concentrations of alendronate, and even beagles dosed with risedronate and tiludronate, which are also bisphosphonates. *See* Exhibit A, "Example 1," col. 14, ln. 9. Additionally, the '329 patent contains detailed observations of the beagle esophagi from each group, including eight full-page

photomicrographs showing a close up view of a representative beagle esophagus from each group. *See* Exhibit A, Figs. 1-8.

16. Merck holds an approved New Drug Application (“NDA No. 20-560”) for alendronate sodium tablets sold under its trademark FOSAMAX®. Merck supplemented NDA No. 20-560 and received approval for 70 mg FOSAMAX® once-weekly tablets for the treatment of osteoporosis, and 35 mg FOSAMAX® once-weekly tablets for the prevention of osteoporosis.

II. The FOSAMAX® Once-Weekly District Court Case

17. Defendant Teva Pharmaceuticals USA, Inc. (“Teva”) filed an abbreviated new drug application (“ANDA”) to gain approval to market generic copies of Merck’s high-dose once-weekly 70 and 35 mg FOSAMAX® once-weekly tablets before the expiration of the ’329 patent. In response, Merck filed suit against Teva for patent infringement in this Court on November 6, 2001. That case became known as *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, (C. A. No. 01-048) (JJF)(the “FOSAMAX® once-weekly case”).

18. In the FOSAMAX® once-weekly case, Teva was represented by the law firm of Kenyon & Kenyon LLP (“Kenyon”).

19. On March 19, 2002, Merck served requests for production on Teva. A copy of “MERCK & CO., INC.’S FIRST SET OF REQUESTS FOR PRODUCTION OF DOCUMENTS AND THINGS (NOS. 1-60) TO DEFENDANT TEVA PHARMACEUTICALS USA, INC.” (“RFPs”) is attached as Exhibit B.

20. Merck’s RFPs sought documents related to Teva’s research and development projects for alendronate. A representative document request from Merck’s RFPs includes the following:

DOCUMENT REQUEST NO. 49 All documents and things relating to research and development of alendronate and

alendronate formulations or any other pharmaceutically active biphosphonate and its formulations.

Exhibit B at 17.

21. Merck's RFPs also requested documents from Teva's parent company, Teva Ltd. (hereinafter, collectively referred to with defendant Teva Pharmaceuticals USA, Inc. as "Teva"). See Exhibit B at 4.

22. In response to Merck's RFPs, Teva produced approximately 4,900 pages of documents, most of which were excerpts from Teva's ANDA. Merck realized that Teva's document production was inadequate, particularly when various Teva witnesses admitted during their depositions that their files had never been searched in connection with the FOSAMAX® once-weekly case. On November 11, 2002, Merck moved to compel production from Teva. Merck's motion to compel was filed under seal because it referred to and contained exhibits of documents that Teva designated as "Highly Confidential" under the applicable protective order.

23. In response to additional requests and communications from Merck, Teva produced a few additional pages of documents. On December 11, 2002, a partner attorney at Kenyon sent a letter (the "Kenyon letter") confirming that Teva had finally complied with Merck's RFPs. In particular, the Kenyon letter states:

As discussed yesterday, I confirm that Teva has conducted a diligent search for documents responsive to Merck's document requests for all persons at Teva involved with the development of Teva's weekly alendronate sodium after the complaint in this action was filed and again after Merck served its document requests on Teva. ... As we have now complied with your requests, we expect that Merck will withdraw it's [sic] motion to compel today.

A copy of the Kenyon letter is attached as Exhibit C.

24. Merck relied upon the assurances in the Kenyon letter, and Merck withdrew its motion to compel. As Merck would later discover, the representations of the Kenyon letter were

false, because Teva continued to withhold highly relevant evidence falling within the scope of Merck's RFPs. As will be discussed below, that evidence would have affected the ultimate outcome of the FOSAMAX® once-weekly case.

III. Trial of the FOSAMAX® Once-Weekly Case

25. Before the bench trial was held in the FOSAMAX® once-weekly case, Merck agreed that it would assert only Claims 23 and 37 of the '329 patent. It was agreed by the parties that if written into independent form, these claims would read as follows:

Claim 23. A method for treating osteoporosis in human comprising orally administering about 70 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

Claim 37. A method for preventing osteoporosis in human comprising orally administering about 35 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

Claim 23 covers Merck's 70 mg FOSAMAX® once-weekly tablets for the treatment of osteoporosis. Claim 37 covers Merck's 35 mg FOSAMAX® once-weekly tablets for the prevention of osteoporosis.

26. A bench trial was held in the FOSAMAX® once-weekly case on March 4-7, 2003. Teva's primary defense was that Merck's patent claims were invalid for anticipation (35 U.S.C. § 102) or obviousness (35 U.S.C. § 103) in light of the April and July 1996 editions of the *Lunar News*, a marketing circular for bone densitometers. The *Lunar News* included a speculative suggestion as to the use of less frequent higher oral doses of alendronate.

27. At the time of the *Lunar News* articles, physicians were concerned about not only the upper gastrointestinal issues surrounding alendronate but also the safety of high oral doses of bisphosphonates. The speculations of the *Lunar News* articles failed to address either of these

concerns, and represented nothing more than an unsupported aspiration that was implausible to the knowledgeable physician.

28. Unlike the *Lunar News* articles, the '329 patent contained Merck's beagle studies and presented data that revealed that less frequent, higher oral doses of alendronate and other bisphosphonates could be given once per week without exacerbating the gastrointestinal side effects, and perhaps with an even better tolerability profile. In contrast, the *Lunar News* articles were nothing more than wishful thinking.

29. Regardless, Teva belittled the beagle studies and argued that they added nothing to the knowledge of those skilled in the art, and therefore added no information beyond the speculations disclosed in the *Lunar News* articles. In its post-trial brief, Teva argued:

The only data that Merck can allege that it had that was not possessed by people of skill in the art in July 1997 are the results of its dog studies. Merck's reliance on these studies is unfounded. **First, the asserted claims are limited to humans, so a result from an experiment on a beagle, whether expected or not, is not relevant. Second, the dog studies provide no data, expected or not, that is relevant to clinical experience.** [p. 45, (emphasis added)]

The dog studies represent a science project. Whether or not they provide interesting information, they do not demonstrate that following the claimed method to treat or prevent osteoporosis provides any results that are "unexpected." [p. 46]

A copy of Teva's Post-Trial Brief is attached as Exhibit D. In its post-trial reply brief, Teva argued:

Although Merck will likely argue that the conclusions of its scientists were bolstered by the results of its dog experiments, that argument does not withstand scrutiny. In May 1997, the only pertinent dog experimental results Merck had were the initial comparisons of the effects of five consecutive exposures to acidic alendronate solution to a single exposure with the same solution. [p. 23]

A copy of Teva's Post-Trial Reply Brief is attached as Exhibit E.

30. On August 23, 2004, this Court issued its Opinion and rejected Teva's arguments and affirmed the validity of Claims 23 and 37 of the '329 patent in light of the *Lunar News* articles. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 288 F.Supp.2d 601 (D.Del. 2003). A copy of this Court's opinion is attached as Exhibit F.

IV. Appeal of the FOSAMAX® Once-Weekly Case

31. Teva appealed to the United States Court of Appeals for the Federal Circuit.

32. Teva stood fast to its rejected arguments that Claims 23 and 37 of the '329 patent were invalid for obviousness in light of the *Lunar News* articles.

33. Once again, Teva argued that the beagle studies added nothing to the knowledge of those skilled in the art, and therefore provided no information beyond the speculations disclosed in the *Lunar News* articles. In its Federal Circuit brief, Teva argued:

Before they [the Merck physicians] filed for the '329 patent they did no clinical research or other testing in humans. ... Thus, they added nothing to the art that was not already set forth in the *Lunar News*. The only data in the patent was generated in beagles whose esophagi were soaked in alendronate solutions for extended periods. [p. 46]

A copy of Teva's Federal Circuit Brief is attached as Exhibit G. In its Federal Circuit Reply brief, Teva argued:

The '329 patent does not include data or reports of experimentation proving the workability of an idea that was contrary to some conventional wisdom. Merck's inventors had no such information. On the contrary, the patent provides nothing beyond what [] had already [been] disclosed in the *Lunar News*. **Specifically, the '329 patent includes no clinical trial data or results from studies in people proving the safety and effectiveness of the once-weekly administration of alendronate.** ... Recognizing this weakness, Merck now feebly attempts to rely on the beagle experiments described in Example 1 in the '329 patent. [p. 18, (emphasis added)]

A copy of Teva's Federal Circuit Reply Brief is attached as Exhibit H.

34. But this time, the outcome was different. A divided panel of the Federal Circuit accepted Teva's arguments, reversed this Court, and held that Claims 23 and 37 of the '329 patent were invalid as obvious in view of the *Lunar News* articles. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). A copy of the Federal Circuit's opinion is attached as Exhibit I.

35. In examining the differences between the *Lunar News* articles and the '329 patent, the Federal Circuit panel majority accepted Teva's arguments, and dismissed the experimental results data obtained from the beagle studies.

The '329 patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent. The only data provided in the '329 patent was generated in beagles, an experiment discredited at trial and disregarded by the district court in its decision. So while the district court may be correct in finding the *Lunar News* articles may have invited skepticism based on concerns for dose-related GI problems, the claimed invention adds nothing beyond the teachings of those articles.

395 F.3d at 1374. *See* Exhibit I.

36. Merck petitioned the Federal Circuit for rehearing and rehearing *en banc*. That petition was denied. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 405 F.3d 1388 (Fed. Cir. 2005). Merck filed a writ of certiorari with the United States Supreme Court, and the writ was denied. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 126 S.Ct. 488 (2005).

V. Teva Withheld Crucial Evidence that Would Have Changed the Outcome of the FOSAMAX® Once-Weekly Case

37. In 2002, Merck granted a license to the Procter & Gamble Co. ("P&G") for Merck patents that cover methods for the oral once-weekly dosing of bisphosphonates, including the methods used in P&G's ACTONEL® (risedronate sodium) once-weekly tablets. Risedronate is also a bisphosphonate, and the license extended to claims of the '329 patent.

38. Teva filed an ANDA to bring a generic copies of P&G's ACTONEL® once-weekly products to the market before the expiration of Merck's patents. As permitted by the terms of the license agreement, Merck sued Teva for patent infringement in the United States District Court for the District of Delaware, in a case known as *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, C.A. No. 04-939 (the "ACTONEL® once-weekly case"). That case is pending, and experts are currently being deposed. Trial is set for late August 2006.

39. On or about April 18, 2006, Merck's counsel reviewed the reports of Teva's experts in the ACTONEL® once-weekly case. In exploring the opinions of Teva's experts, Merck's counsel searched the publicly available patents and applications available from the web site of the United States Patent and Trademark Office ("PTO"). Specifically, Merck's counsel sought any patents or applications assigned to Teva that related to dosing of bisphosphonates.

40. Merck's counsel found a Teva patent application that had been withheld from Merck during the FOSAMAX® once-weekly case. Teva's withheld patent application reflected that Teva performed its own beagle studies, for which the underlying documents have also been withheld. On December 16, 2002, Teva filed a provisional patent application with the PTO entitled "METHOD OF INCREASING BIOAVAILABILITY OF ALENDRONATE OR OTHER BISPHOSPHONATES BY PREDOSE ADMINISTRATION OF ALFACALCIDOL," which was assigned application No. 60/433,685 (the "'685 application"). The withheld '685 application is generally directed to a method for giving a dose of a form of Vitamin D at least six hours before giving a dose of alendronate, which will purportedly increase the bioavailability of alendronate. A copy of the '685 application is attached as Exhibit J.

41. The '685 application relates to the technology that was in dispute during the FOSAMAX® once-weekly case, and falls within the scope of Merck's RFPs. *See* Paragraph 20. Yet Teva withheld it from Merck during the FOSAMAX® once-weekly case.

42. Teva withheld the '685 application even though the same lawyers who were trial counsel in the FOSAMAX® once-weekly case filed the '685 application on Teva's behalf. Moreover, the filing date of the '685 application indicates that the representations in the Kenyon letter were manifestly false.

43. On December 16, 2002, five days after the Kenyon letter, Teva filed the '685 application with the United States Patent and Trademark Office. Considering the experiments described in the '685 application took weeks to perform, documents related to the '685 application existed. Any doubt about the relevance of the '685 application is immediately dispelled by its statement that "the therapeutically effective dose of alendronate administered is ... especially between about 10 mg and about 70 mg." *See* Exhibit J at 4. Merck sued Teva in the FOSAMAX® once-weekly case because Teva sought to commercialize generic copies of Merck's 35 and 70 mg FOSAMAX once-weekly tablets.

44. The content of the withheld '685 application includes statements that directly contradict Teva's arguments to this Court and the Federal Circuit. The most egregious of these statements is the revelation that Teva had conducted its own beagle studies to support alendronate dosing patents. *See* Exhibit J at 8.

45. As stated above, Teva dismissed the value of the beagle experiments in the '329 patent during the FOSAMAX® once-weekly case, and argued that the dog studies in the '329 patent "added nothing to the prior art" over the disclosures of the *Lunar News*. Teva argued that Merck "feebly" attempted "to rely on the beagle experiments described in Example 1 of the '329

patent,” because the ’329 patent contains “no clinical trial data or results from studies in people proving the safety and effectiveness of the once-weekly administration of alendronate.” Yet in the ’685 application, Kenyon attorneys had submitted Teva’s very own beagle studies to the PTO in support of Teva’s patent application for methods for dosing alendronate. In the single “Example” of the ’685 application, Teva performed oral alendronate experiments in “an *in vivo* study in an animal model” using “six female beagle dogs.” See Exhibit J at 8.

46. By withholding the ’685 application, Teva deprived Merck of the opportunity to depose Teva’s inventors about their oral alendronate experiments involving beagles. Teva also deprived Merck of the opportunity to analyze Teva’s data, experimental techniques, and laboratory information. In contrast, Merck complied with its discovery obligations and provided Teva with access to the scientists who performed the beagle studies, as well as Merck’s scientific and laboratory information underlying Merck’s beagle studies.

47. The FOSAMAX® once-weekly case was a classic “close case.” Judge Farnan, the PTO, and Judge Rader agreed with Merck, while the two other judges on the Federal Circuit panel agreed with Teva. In such a close case, Teva’s withheld beagle studies would have been crucial evidence that would have affected the outcome of the FOSAMAX® once-weekly case.

VI. Teva’s Pattern of Discovery Abuse

48. In addition to Merck’s motion to compel and the recently discovered ’685 patent application, other aspects of Teva’s document production from the FOSAMAX® once-weekly case demonstrate that Teva failed to comply with Merck’s RFPs.

49. During post-trial briefing in the FOSAMAX® once-weekly case, counsel for Merck discovered U.S. Patent No. 6,476,006 (the “’006 patent”) assigned to Teva. The ’006 patent was generally directed to delayed-release dosage forms for bisphosphonates, including

alendronate. Just like the '685 patent, Teva withheld the '006 patent from Merck during the FOSAMAX® once-weekly case. The '006 patent also contradicts Teva's arguments that claims 23 and 37 are obvious in light of the *Lunar News*. And like the '685 application, Kenyon filed this application on behalf of Teva. Merck moved to add the '006 patent to the trial record, and a copy of Merck's motion is attached as Exhibit K. The '006 patent was attached as Exhibit A to that motion. This Court granted Merck's motion.

50. Just before this Court issued its opinion in the FOSAMAX® once-weekly case, counsel for Merck discovered another Teva patent application that Teva withheld from Merck. PCT patent application WO 03/057/136 (the "'136 application") was published on July 17, 2003. The '136 application claimed priority from an application filed on December 24, 2001, and once again, Kenyon was the prosecuting law firm. The '136 application relates to tablets sheathed with a powder or granulous layer to prevent contact with irritating ingredients at the center of the tablet. Alendronate is one of the irritating ingredients disclosed in the '136 application. Again, these statements contradict the arguments Teva made throughout the FOSAMAX® once-weekly case. Merck also moved to add the '136 application to the trial record, but this Court did not rule on that motion. A copy of that motion is attached as Exhibit L. The '136 application was attached as Exhibit A to that motion.

51. In the ACTONEL® once-weekly case, Teva also failed to produce the '685 application and any underlying data, including data from Teva's beagle experiments, even though Merck served the following document requests on Teva:

Request for Production No. 44 All documents and things relating to Defendant's research and development of tablets containing risedronate.

Request for Production No. 45 All documents and things relating to patent applications, including the patents themselves, filed in

any country by Defendant referencing, referring, or relating to risedronate.

Exhibit M at 25. In the '685 application, Teva told the PTO that "the bisphosphonates useful in the practice of the present invention include ... risedronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "risedronate")." *See* Exhibit J at 6.

52. The '006 patent, the '136 application, and the '685 application are Teva's patent filings, and specifically refer to risedronate in addition to alendronate. All of these were filed and prosecuted by Teva's litigation counsel Kenyon. Even though all of these fall within the scope of Merck's document requests in the ACTONEL® once-weekly case, Teva has failed to produce them.

53. Considering Teva's repeated failure to produce highly relevant documents, Teva has an intentional strategy to withhold documents that contradict Teva's litigation arguments and support Merck's positions.

54. Teva still has not produced any of the experimental data underlying the '685 application, including data from Teva's beagle experiments with oral alendronate.

55. Teva must possess many more relevant documents beyond the '685 application that were never produced during the FOSAMAX® once-weekly case, including documents that Merck is still unaware of.

56. Teva's repeated withholding of evidence and knowing misrepresentations to the Federal Circuit, this Court, and Merck erroneously caused claims 23 and 37 of the '329 patent to be rendered invalid in the FOSAMAX® once-weekly case in a grave miscarriage of justice.

COUNT 1

57. Merck realleges paragraphs 1 through 56 above as if fully set forth herein.

58. Through Teva's fraud and misconduct in failing to produce documents reflecting Teva's own beagle experiments with oral alendronate and other documents such as the '685 application and its file history, Teva caused a grave miscarriage of justice that resulted in Claims 23 and 37 of the '329 patent being rendered invalid.

59. Through knowingly misrepresenting that it had complied with Merck's RFPs, Teva effectuated a fraud or other misconduct upon this Court, the Federal Circuit, and Merck that caused a grave miscarriage of justice that resulted in Claims 23 and 37 of the '329 patent being rendered invalid.

60. Pursuant to Rule 60(b) of the Federal Rules of Civil Procedure, it is requested that this Court vacate the judgment entered in the FOSAMAX® once-weekly case holding Claims 23 and 37 of the '329 patent invalid, or grant any other appropriate relief from that judgment because of Teva's fraud, misrepresentation, and other misconduct.

COUNT 2

61. Merck realleges paragraphs 1 through 56 above as if fully set forth herein.

62. Through Teva's fraud, misrepresentations, or other misconduct in the FOSAMAX® once-weekly case, Teva caused a grave miscarriage of justice.

63. The findings from the Federal Circuit decision in the FOSAMAX® once-weekly case infect other litigations, including the ACTONEL® once-weekly case, and thus further the grave miscarriage of justice that Teva caused in the FOSAMAX® once-weekly case.

64. It is requested that this Court enjoin Teva from asserting any estoppel based upon the findings from the Federal Circuit's opinion in the FOSAMAX® once-weekly case.

REQUESTED RELIEF

Plaintiff Merck respectfully requests the following relief:

- a. To vacate the judgment entered in the FOSAMAX® once-weekly case holding Claims 23 and 37 of the '329 patent invalid, or any other appropriate relief from that judgment;
- b. That the Court enjoin Teva, its officers, agents or attorneys and employees, and those acting in privity or in concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of alendronate sodium and any therapeutic composition covered by Claims 23 and 37 of the '329 patent.
- c. That the Court enjoin Teva from asserting any estoppel based upon the findings from the Federal Circuit's opinion in the FOSAMAX® once-weekly case;
- d. That Teva pay all of Merck's costs and attorneys' fees in bringing the FOSAMAX® once-weekly case;
- e. That Teva pay all of Merck's costs and attorneys' fees in bringing this litigation; and
- f. That this Court award such other and further relief as the Court may deem just and equitable.

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519836

EXHIBIT A

US005994329A

United States Patent [19][11] **Patent Number:** **5,994,329****Daifotis et al.**[45] **Date of Patent:** **Nov. 30, 1999**[54] **METHOD FOR INHIBITING BONE RESORPTION**[75] Inventors: **Anastasia G. Daifotis**, Westfield;
Arthur C. Santora, II, Watchung; **A. John Yates**, Westfield, all of N.J.[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.[21] Appl. No.: **09/134,214**[22] Filed: **Aug. 14, 1998****Related U.S. Application Data**

[63] Continuation of application No. PCT/US98/14796, Jul. 17, 1998.

[60] Provisional application No. 60/053,535, Jul. 23, 1997, and provisional application No. 60/053,351, Jul. 22, 1997.

[51] **Int. Cl.**⁶ **A61K 31/66**[52] **U.S. Cl.** **514/108**[58] **Field of Search** 514/108[56] **References Cited****U.S. PATENT DOCUMENTS**

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(List continued on next page.)

Primary Examiner—Theodore J. Criares*Attorney, Agent, or Firm*—Anthony D. Sabatelli; Melvin Winokur[57] **ABSTRACT**

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

44 Claims, 8 Drawing Sheets

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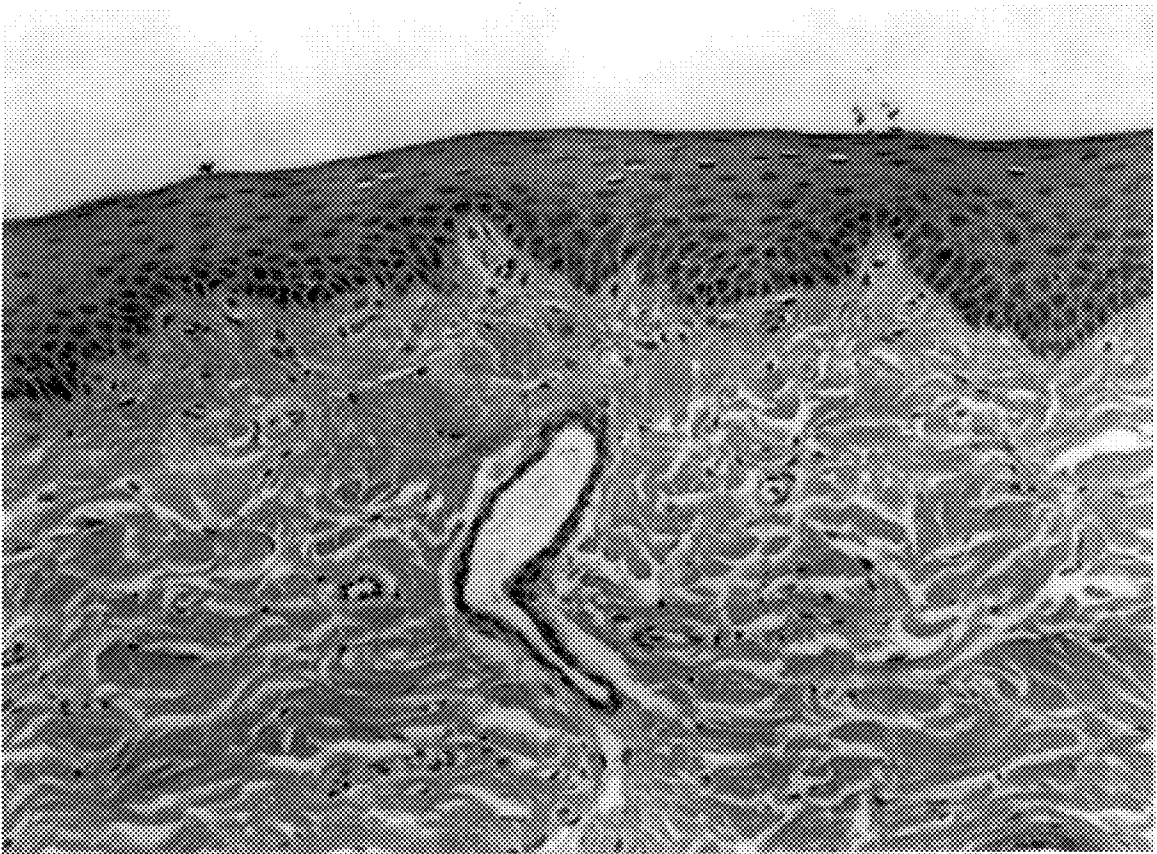


FIG. 1

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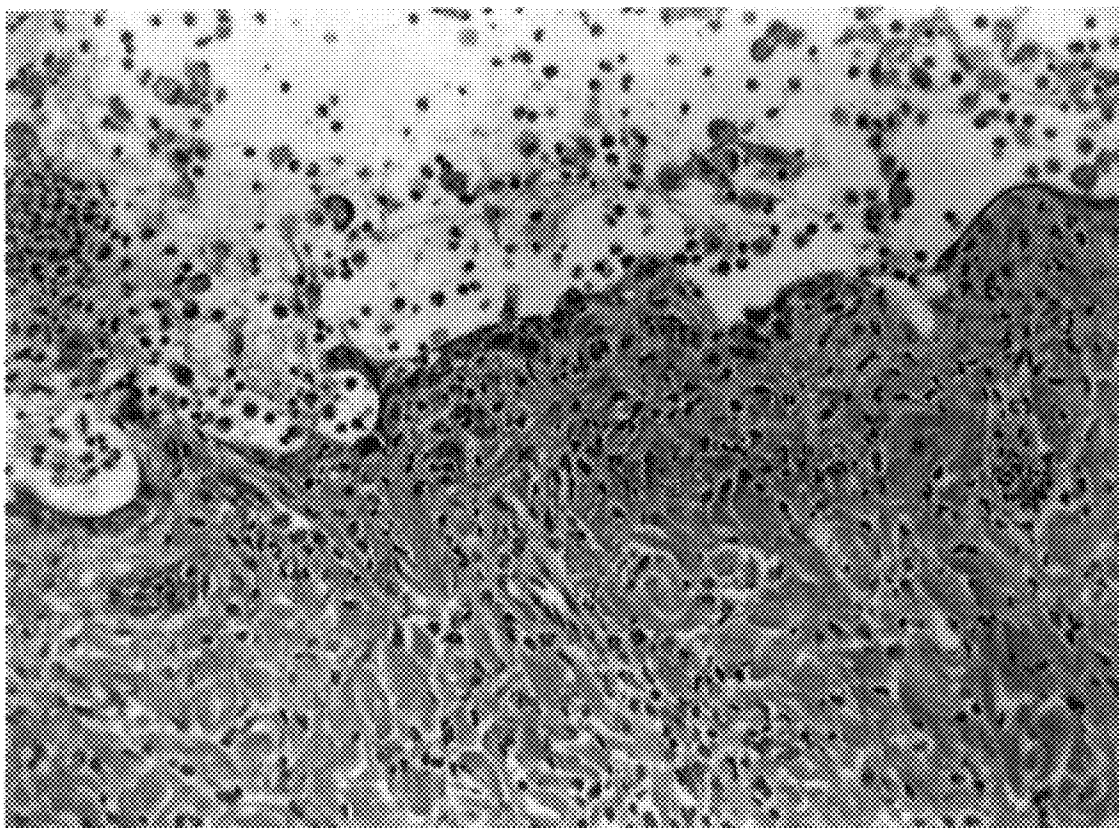


FIG.2

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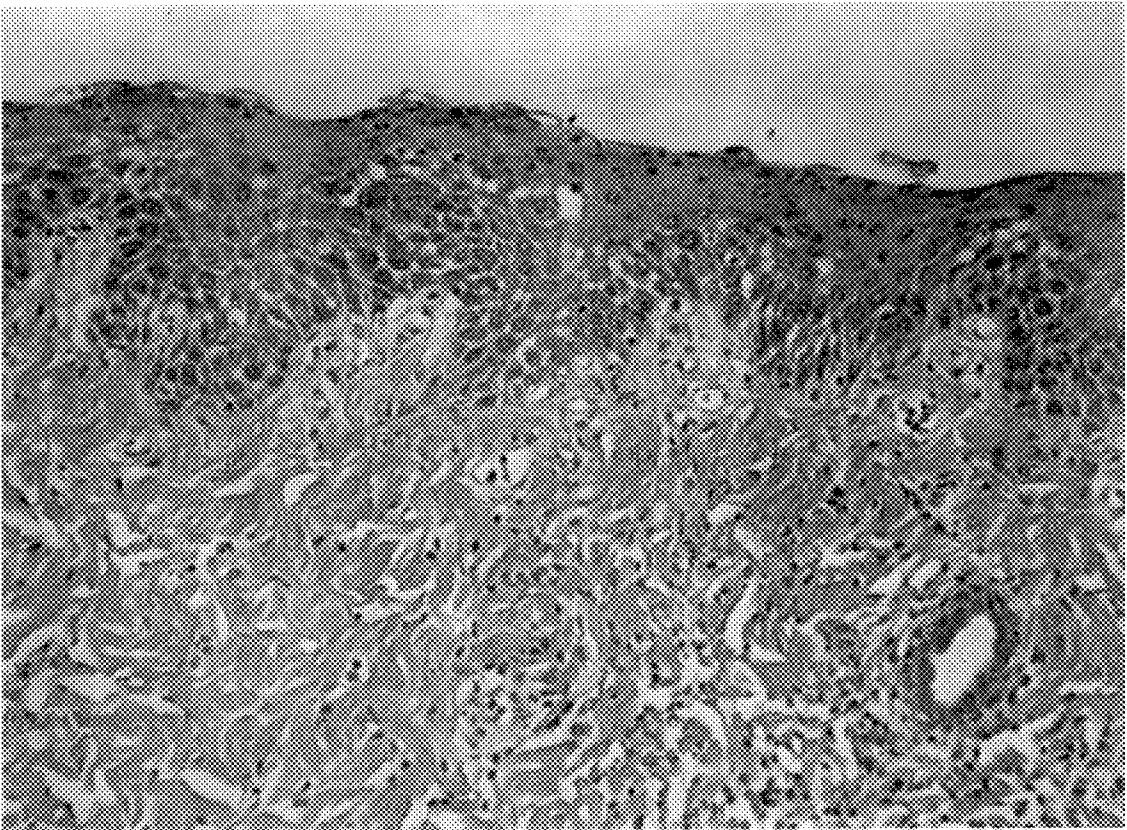


FIG.3

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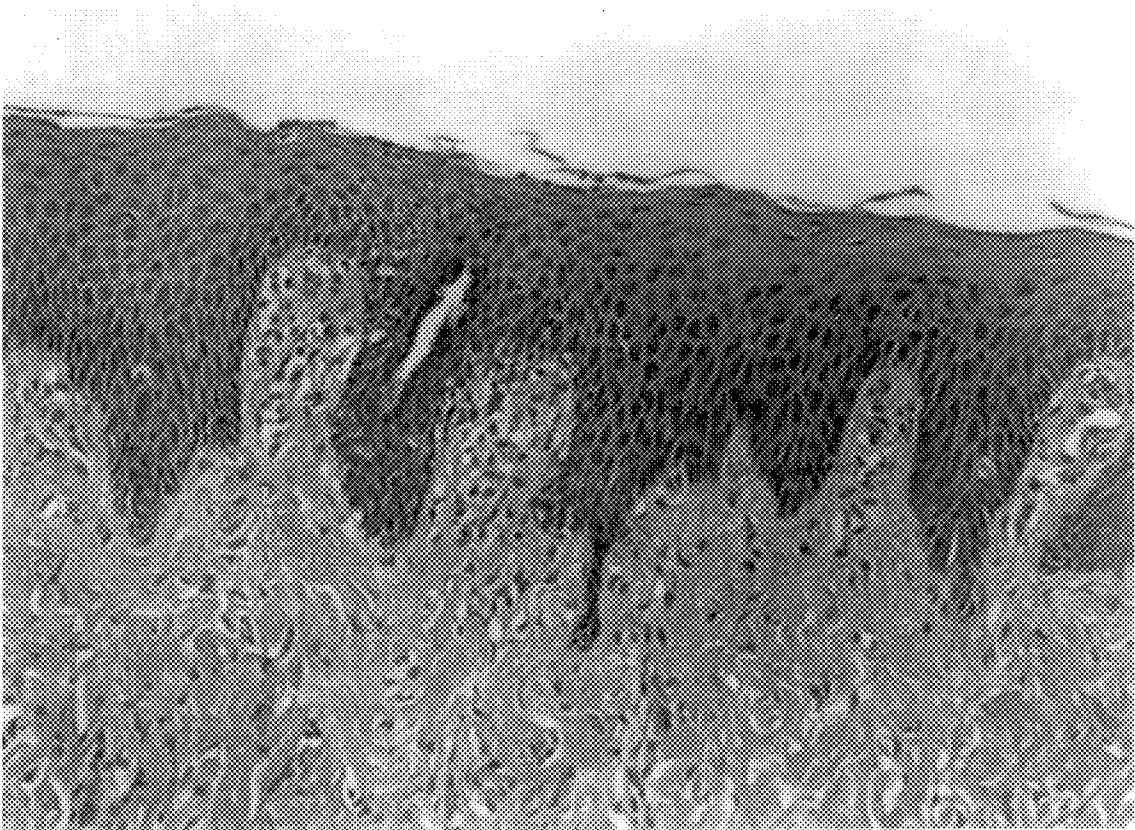


FIG. 4

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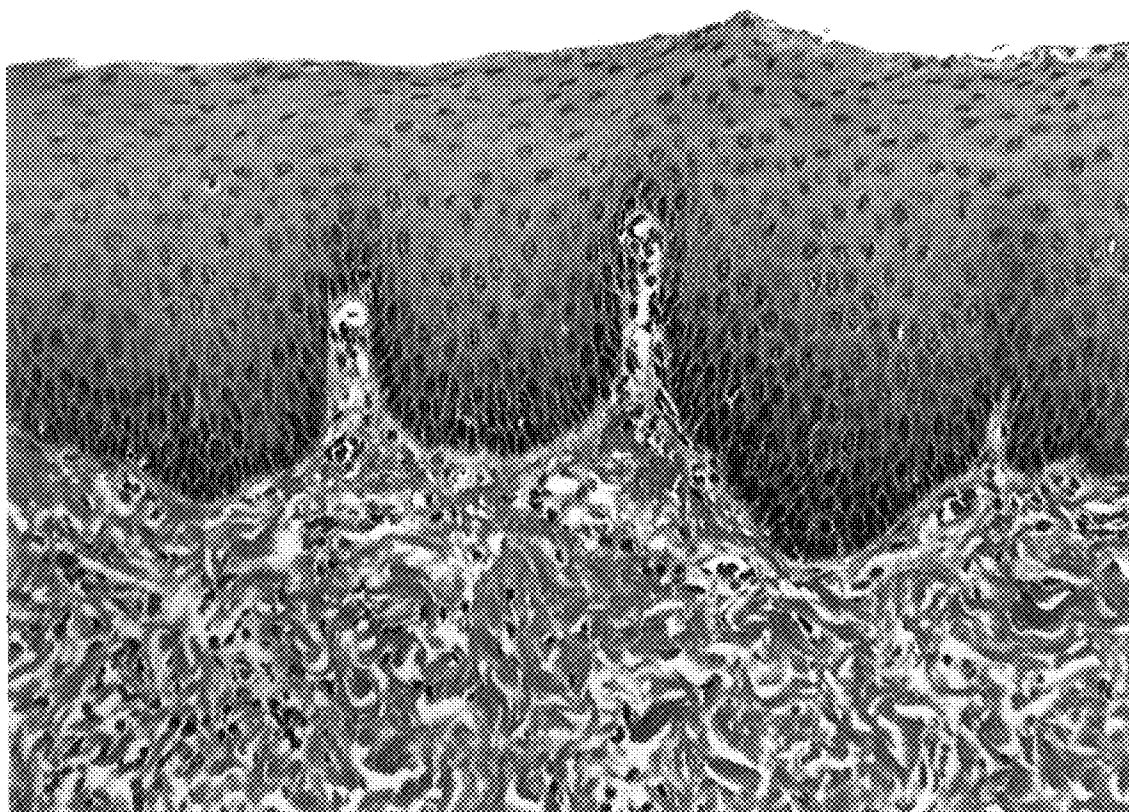


FIG.5

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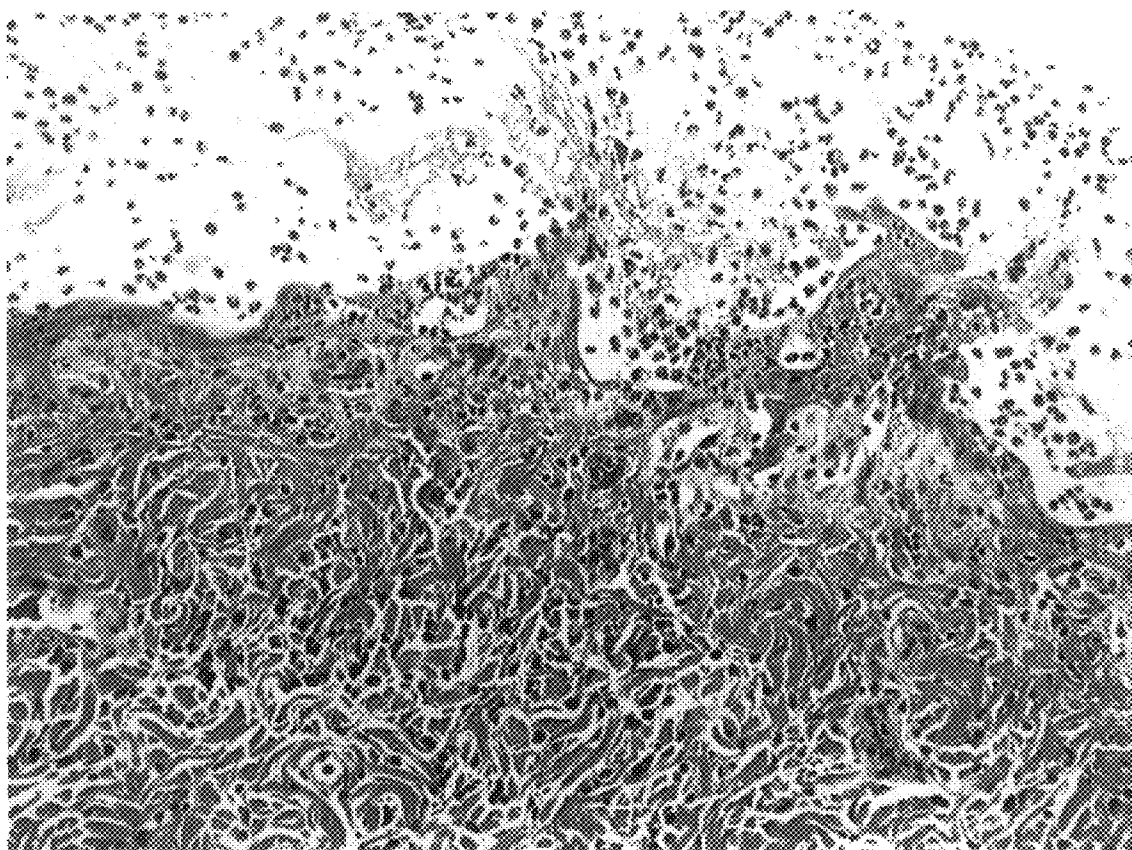


FIG.6

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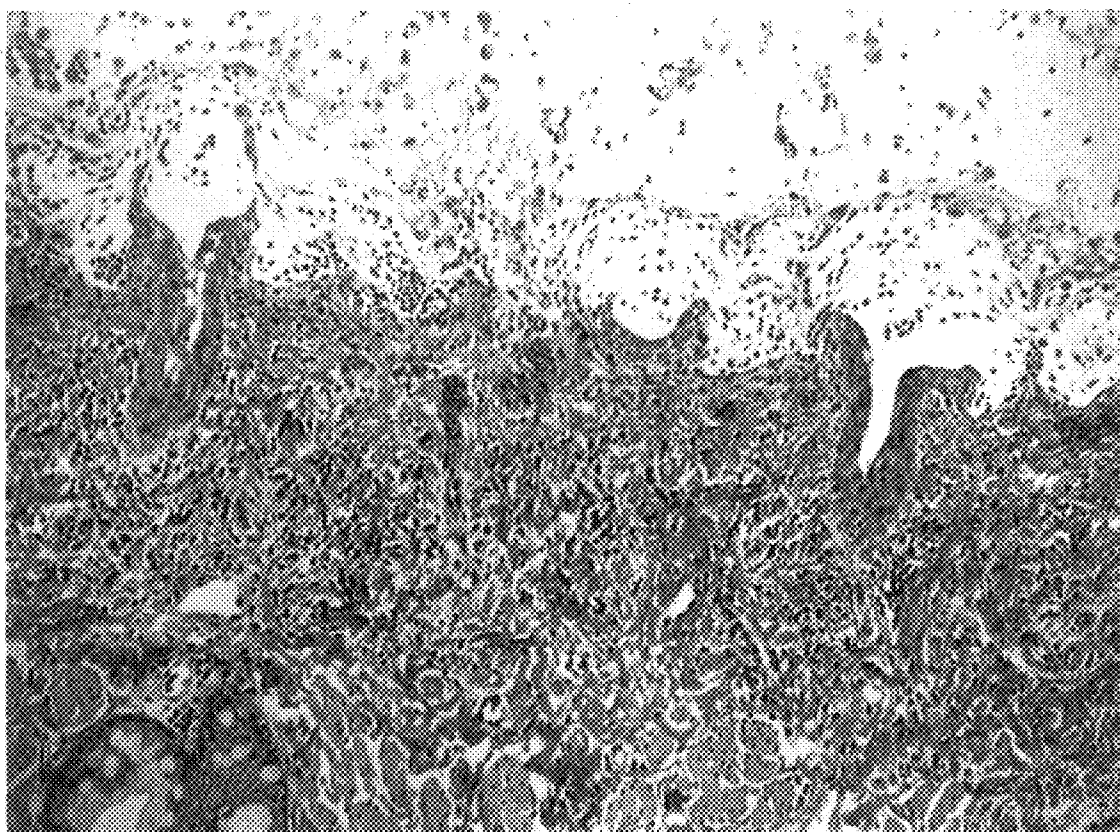


FIG.7

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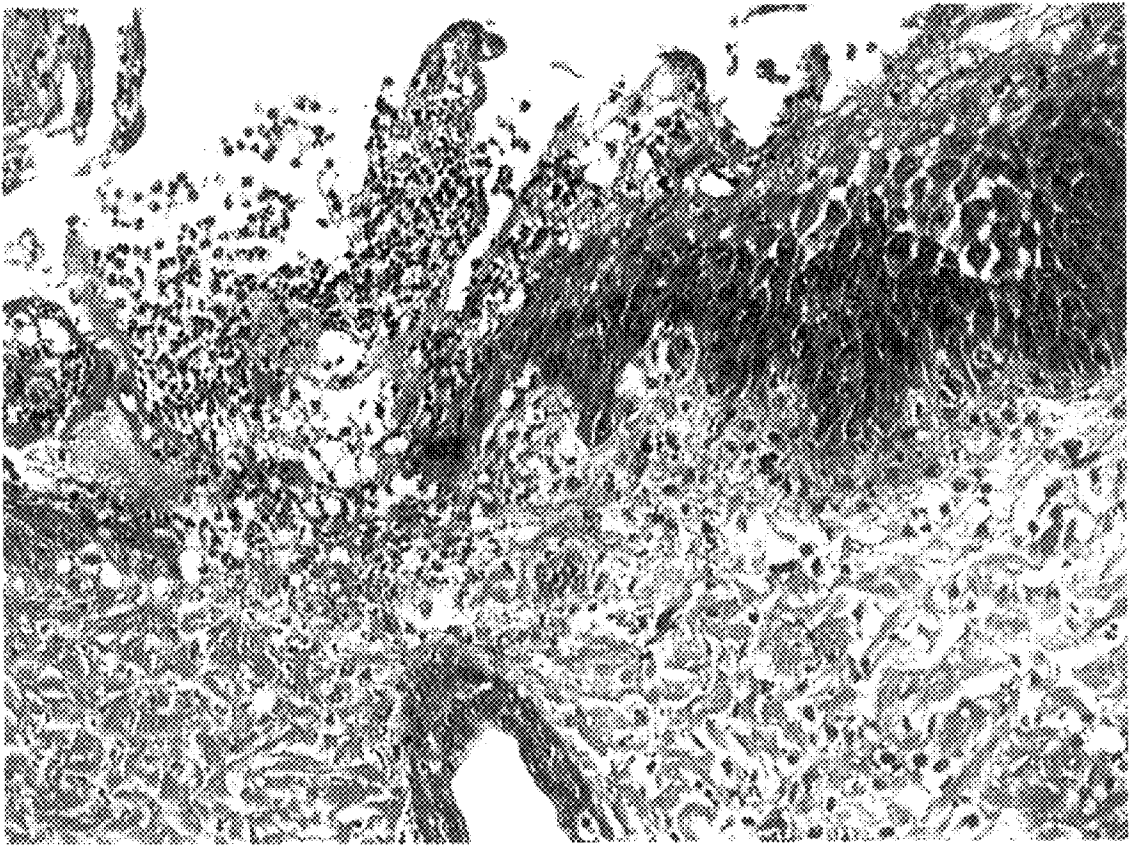


FIG.8

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METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/US98/14796, filed Jul. 17, 1998, and also claims priority to U.S. provisional applications Serial Nos. 60/053,535, filed Jul. 23, 1997, and 60/053,351, filed Jul. 22, 1997, both now abandoned, the contents of all of the foregoing of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to oral methods for inhibiting bone resorption in a mammal while minimizing the occurrence of or potential for adverse gastrointestinal effects. These methods comprise orally administering to a mammal in need thereof of a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The present invention also relates to pharmaceutical compositions and kits useful for carrying out these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient*, 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zoledronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) *Lancet* 1(8381), pp. 821-824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) *Br. Med. J.* 292, pp.

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1227-1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B. J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.*, Suppl. 3:S13-16 (1993) and B. J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics*, vol. 58, number 3, pp. 288-298 (September 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E. G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320-322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P. C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016-1021 (1996), D. O. Castell, *Pill Esophagitis—The Case of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1058-1059 (1996), and U. A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1069-1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C. H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144-152, (August 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because

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bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Pat. No. 4,761,406, to Flora et al, issued Aug. 2, 1988, which is incorporated by reference herein in its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate*, *Journal of Bone and Mineral Research*, vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Pat. No. 5,366,965, to Strein, issued Nov. 22, 1994, which is incorporated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.

It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administra-

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tion of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a function of increasing bisphosphonate dosage. Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastrointestinal effects.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

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SUMMARY OF THE INVENTION

The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosages according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

In other embodiments, the present invention relates to such methods useful in humans.

In other embodiments, the present invention relates to such methods useful in humans identified as having or being susceptible to upper gastrointestinal disorders.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered on five consecutive days.

FIG. 2 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated gastric juice administered on five consecutive days.

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FIG. 3 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 4 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 5 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

FIG. 6 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3–4 days.

FIG. 7 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

FIG. 8 is a photomicrograph (total magnification 270×) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric juice administered on five consecutive days.

DESCRIPTION OF THE INVENTION

The present invention relates to a method, preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects. The present invention relates to methods of treating or preventing abnormal bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal.

The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

The methods of the present invention are generally administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human patients in need of inhibiting bone

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resorption, such as patients in need of treating or preventing abnormal bone resorption.

The administration methods of the present invention are especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia, ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

The term "minimize the occurrence of or potential for adverse gastrointestinal effects", as used herein, means reducing, preventing, decreasing, or lessening the occurrence of or the potential for incurring unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the upper gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with more normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

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Methods of the Present Invention

The present invention comprises methods for inhibiting bone resorption in mammals. The present invention also comprises treating abnormal bone resorption in mammals.

5 The present invention also comprises methods for preventing abnormal bone resorption in mammals. In preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause or increase the potential for adverse gastrointestinal effects or which require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

10 By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit

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dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occurred in proximity to a prosthetic implant).

Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

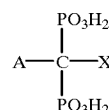
The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published Nov. 16, 1995, which is incorporated by reference herein in its entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula

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wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C1-C30 substituted alkyl, C1-C10 alkyl or dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl or phenyl substituted thio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH₂, C1-C10 alkyl or dialkyl substituted NH₂, OH, SH, and C1-C10 alkoxy.

In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, halogen, and C1-C10 alkyl or phenyl substituted thio.

More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1,1-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting of alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the

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present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Pat. No. 4,922,007, to Kieczkowski et al., issued May 1, 1990, and U.S. Pat. No. 5,019,651, to Kieczkowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem.* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Pat. No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (pidronate) is described in U.S. Pat. No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248, to Breliere et al., Oct. 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, pidronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate. Pharmaceutical Compositions

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers,

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collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, buffers, coatings, and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Pat. No. 5,358,941, to Bechard et al, issued Oct. 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide, and the like.

The precise dosage of the bisphosphate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 $\mu\text{g/kg}$ body weight and preferably about 10 to about 2000 $\mu\text{g/kg}$ of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit

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dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L. J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease*, Arch. Intern. Med., vol. 152, pp. 726-732 (April 1992), which is incorporated by reference herein in its entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphosphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

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EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

Esophageal Irritation Potential

The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

The following solutions are prepared:

- (1) simulated gastric juice (pH about 2), i.e. the control solution.
- (2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (4) simulated gastric juice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.
- (6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3 mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

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Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.

Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.

Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 1 is a representative photomicrograph from a Group 1 animal.

For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 2 is a representative photomicrograph from a Group 2 animal.

For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. 3 is a representative photomicrograph from a Group 3 animal.

For the Group 4 animals, the photomicrographs show that the esophagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. 4 is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

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For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 5 is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 6 is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 7 is a representative photomicrograph from a Group 7 animal.

For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. 8 is a representative photomicrograph from a Group 8 animal.

These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1) is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate considerably less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

TABLE 1

Esophageal Irritation Potential Studies				
Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n = 4)	0	1x daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n = 4)	Alendronate 0.20	1x daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n = 5)	Alendronate 0.80	1x	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n = 5)	Alendronate 0.80	1x	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n = 6)	Alendronate 0.80	1x weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.
6 (n = 6)	Alendronate 0.40	2x weekly for 4 weeks	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.

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TABLE 1-continued

Esophageal Irritation Potential Studies				
Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
7 (n = 8)	Risedronate 0.20	1× daily for 5 days	immediate ly after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n = 4)	Tiludronate 4.0	1× daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

Example 2

Once-weekly dosing regimen.
Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 3

Twice-weekly dosing regimen.
Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or

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four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 4

Biweekly dosing regimen
Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 5

Twice-monthly dosing regimen.
Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing other disorders associated with abnormal bone resorption.

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In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2–5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68mg	182.72g
Anhydrous Lactose, NF	71.32mg	285.28g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation.

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1N Sodium Hydroxide (aq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g.

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about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A method for inhibiting bone resorption in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

3. A method according to claim 2 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

4. A method according to claim 3 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

5. A method according to claim 2 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

6. A method according to claim 4 wherein said mammal is a human.

7. A method according to claim 6 wherein said dosing interval is once-weekly.

8. A method according to claim 7 wherein said unit dosage of said bisphosphonate comprises from about 17.5 mg to about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

9. A method according to claim 8 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

10. A method according to claim 6 wherein said dosing interval is twice-weekly.

11. A method according to claim 10 wherein said unit dosage of said bisphosphonate comprises from about 8.75 mg to about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

12. A method according to claim 6 wherein said dosing interval is biweekly.

13. A method according to claim 12 wherein said unit dosage of said bisphosphonate comprises from about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

14. A method according to claim 6 wherein said dosing interval is twice-monthly.

15. A method according to claim 14 wherein said unit dosage of said bisphosphonate comprises about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

16. A method for treating osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting

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of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

17. A method according to claim 16 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, 5 etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

18. A method according to claim 17 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof. 10

19. A method according to claim 18 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

20. A method according to claim 17 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

21. A method according to claim 19 wherein said mammal 20 is a human.

22. A method according to claim 21 wherein said dosing interval is once-weekly.

23. A method according to claim 22 wherein said unit dosage of said bisphosphonate comprises about 70 mg of 25 alendronate monosodium trihydrate, on an alendronic acid active basis.

24. A method according to claim 21 wherein said dosing interval is twice-weekly.

25. A method according to claim 24 wherein said unit dosage of said bisphosphonate comprises about 35 mg of 30 alendronate monosodium trihydrate, on an alendronic acid active basis.

26. A method according to claim 21 wherein said dosing interval is biweekly.

27. A method according to claim 26, wherein said unit dosage of said bisphosphonate comprises about 140 mg of 35 alendronate monosodium trihydrate, on an alendronic acid active basis.

28. A method according to claim 21 wherein said dosing interval is twice-monthly. 40

29. A method according to claim 28 wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

30. A method for preventing osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule 45 having a dosing interval selected from the group consisting

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of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

31. A method according to claim 30 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, 5 etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

32. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

33. A method according to claim 32 wherein said pharmaceutically acceptable salt is alendronate monosodium 15 trihydrate.

34. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

35. A method according to claim 33 wherein said mammal is a human.

36. A method according to claim 35 wherein said dosing interval is once-weekly.

37. A method according to claim 36 wherein said bisphosphonate unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

38. A method according to claim 35 wherein said dosing interval is twice-weekly.

39. A method according to claim 38 wherein said bisphosphonate unit dosage comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

40. A method according to claim 35 wherein said dosing interval is biweekly.

41. A method according to claim 40 wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

42. A method according to claim 35 wherein said dosing interval is twice-monthly.

43. A method according to claim 42 wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

44. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * * *

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,

Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC

Defendant.

C.A. No. 01-048-JJF
(Consolidated)

**MERCK & CO., INC.'S FIRST SET OF REQUESTS
FOR PRODUCTION OF DOCUMENTS AND THINGS (NOS. 1-60)
TO DEFENDANT TEVA PHARMACEUTICALS USA, INC.**

Pursuant to Rule 34 of the Federal Rules of Civil Procedure, Plaintiff Merck & Co., Inc. ("Merck") requests that Defendant Teva Pharmaceuticals USA, Inc. produce for inspection and copying the following documents and things in their possession, custody, or control. The requested documents and things are to be made available for inspection, copying, and/or photographing at the offices of HOWREY SIMON ARNOLD & WHITE, LLP, 750 Bering Drive, Houston, Texas 77057, thirty (30) days after the service hereof, or at such other time and location as may be mutually agreed upon by the parties. Documents either shall be produced as required by Rule 34.

DEFINITIONS AND INSTRUCTIONS

The following definitions and instructions are applicable to terms employed in this set of requests:

A. These requests require you to produce all documents and things that are in your actual or constructive possession, custody, or control or in the possession, custody or control of your attorneys, accountants, representatives, consultants, agents, employees, or anyone else acting on your behalf.

B. The term "DOCUMENT" shall have the broadest meaning possible under the Federal Rules of Civil Procedure and shall include, but not be limited to, the original (or a copy when the original is not available), each non-identical copy (including those which are non-identical by reason of notations or markings, or by appearing in the files of a separate person), and any books, notebooks, pamphlets, periodicals, letters, reports, memoranda, handwritten notes, notations, messages, telegrams, wires, cables, press or news wire releases, records, studies, analyses, summaries, magazines, booklets, circulars, labels, catalogs, bulletins, instructions, operating or maintenance manuals, operating or product specifications, fabrication sheets, calendars, day-timers, notes or records of meetings, notices, purchase orders, bills, ledgers, checks, tabulations, questionnaires, surveys, drawings, sketches, schematics, blueprints, flow sheets, working papers, charts, graphs, indices, tapes, agreements, releases, appraisals, valuations, estimates, opinions, financial statements, accounting records, income statements, photographs, films or videotapes, tapes, minutes, contracts, leases, invoices, records of purchase or sale, correspondence, electronic or other transcription or taping of or notes pertaining to telephone or personal conversations or conferences, tape recordings, electromagnetic recordings, voice mail messages or transcriptions thereof, interoffice and intraoffice communications of all types, E-mail messages or printouts thereof, microfilms, CD ROMs, videotapes or cassettes, films, movies, computer printouts and all other written, printed, typed, punched, engraved, taped, filmed, recorded (electronically or otherwise), labeled, or graphic matter or thing, of whatever description, however produced or reproduced (including computer-stored or generated data, together with instructions or programs necessary to search and retrieve such data), and shall include all attachments to (including tangible things) and enclosures with (including tangible

things) any requested item, to which they are attached or with which they are enclosed, and each draft thereof.

C. The term "THING" refers to any tangible object, other than a DOCUMENT, and includes objects of every kind and nature including, but not limited to, prototypes, models, samples and specimens.

D. These requests shall include DOCUMENTS and THINGS created, acquired, or identified up to the date(s) of production and shall be deemed to be continuing. Therefore, Defendant shall promptly produce to Merck, as supplemental responses to these requests in accordance with FED. R. CIV. P. 26(e), any additional DOCUMENTS or THINGS that Defendant identify, acquire, or become aware of up to and including the time of trial.

E. The term "communications" includes all discussions, conversations, interviews, negotiations, facsimiles, cablegrams, mailgrams, telegrams, telexes, cables or other forms of written or verbal interchange, however transmitted, including reports, notes, memoranda, lists, agenda, and other documents and records of communications, and when used shall require a statement of the name of the individual who made the communication, the person(s) to whom he made it, the date it was made, the form in which it was made, and whether or not it was recorded.

F. Where identification of a DOCUMENT or THING is requested, such identification should be sufficient for the characterization of the DOCUMENT or THING in a request by Merck for production of DOCUMENTS under Rule 34 of the Federal Rules of Civil Procedure and should include, without limitation, the following information:

1. identification of the author or maker;
2. the date that the DOCUMENT or THING was generated;

3. the general nature of the DOCUMENT or THING, i.e., whether it is a letter, a memorandum, a photograph, etc.;
4. identification of the PERSON to whom the original was addressed;
5. identification of all recipients;
6. the identity of the PERSON now having possession of the original DOCUMENT or THING and the location of the original; and
7. the identity of each PERSON now having possession of a copy of the DOCUMENT or THING and the location of each such copy.

G. The word “PERSON” or “PERSONS” shall mean an individual, corporation, proprietorship, partnership, association, joint venture, or any other entity.

H. Where identification of a PERSON is required, such identification shall, without limitation, include the following information:

1. the PERSON’s full name;
2. whether it is an individual, corporation, proprietorship, partnership, association, or other entity;
3. current or last known business address;
4. if the PERSON is an individual, the individual’s home address, or if it is not known, the individual’s last known home address; and
5. if the PERSON is an individual, the individual’s present employer and position.

I. “Teva USA” shall mean Teva Pharmaceutical USA, Inc., and shall include (a) any divisions, departments, parents, subsidiaries, other organizational or operational units, and agents of Teva Pharmaceutical USA, Inc.; (b) all predecessor or successor companies or corporations; (c) all companies, corporations, partnerships, associations, or other business entities which are or have been under the common ownership or control, in any manner, Teva Pharmaceutical USA, Inc. and (d) each of the present and former officers, directors, employees, agents, attorneys, or other representatives of any of them.

J. “Defendant” shall mean Teva USA.

K. In the event Defendant claims that a request is overly broad, Defendant is requested to respond to that portion of the request which is unobjectionable and specifically identify the respect in which the request is allegedly overly broad.

L. In the event Defendant claims that a request is unduly burdensome, Defendant is requested to respond to that portion of the request which is unobjectionable and specifically identify the respect in which the request is allegedly unduly burdensome.

M. With respect to any DOCUMENT or THING that Defendant is unwilling to produce for inspection by Merck’s counsel because the DOCUMENT or THING is asserted to be immune from discovery under the attorney-client privilege or work-product immunity, state separately with respect to each such DOCUMENT or THING sufficient information to disclose:

1. the general nature of each such DOCUMENT and/or THING, i.e., whether it is a letter, memorandum, report, pamphlet, etc.;
2. the date on which each such DOCUMENT and/or THING was reproduced or transcribed;
3. the name and business address of the PERSON who signed or prepared each such DOCUMENT and/or THING or both and the name and business address of each such PERSON who has edited, corrected, revised, or amended the same;
4. the name and business address of each PERSON to whom any such DOCUMENT or THING was given or sent, or otherwise known to Defendant as being an intended or actual recipient of a copy thereof;
5. the name and address of the PERSON having possession, custody, or control of each such DOCUMENT or tangible THING;
6. a brief indication of the subject matter of each such DOCUMENT or THING; and
7. the grounds for the claimed privilege or immunity as to each such DOCUMENT or THING.

N. For any requested DOCUMENT that has been destroyed after January 25, 2001, Defendant shall identify each DOCUMENT, set forth the contents of each destroyed DOCUMENT, the date of such destruction, the identity of any individuals who authorized the destruction, and other circumstances related to such destruction.

O. “The term ‘077 patent” refers to U.S. Patent No. 4,621,077, entitled “Pharmacologically Active Biphosphonates, Process for the Preparation Thereof and Pharmaceutical Compositions Therefrom.”

P. “The term ‘941 patent” refers to U.S. Patent No. 5,358,941, entitled “Dry Mix Formulation for Bisphosphonic Acids with Lactose.”

Q. “The term ‘590 patent” refers to U.S. Patent No. 5,681,590, entitled “Dry Mix Formulations for Bisphosphonic Acids.”

R. “The term ‘726 patent” refers to U.S. Patent No. 5,849,726, entitled “Anhydrous Alendronate Monosodium Salt Formulations.”

S. “The term ‘207 patent” refers to U.S. Patent No. 6,008,207, entitled “Anhydrous Alendronate Monosodium Salt Formulations.”

T. “The ‘410 patent” refers to U.S. Patent No. 6,090,410, entitled “Dry Mix Formulations for Bisphosphonic Acids.”

U. “The ‘329 patent” refers to U.S. Patent No. 5,994,329, entitled “Method for Inhibiting Bone Resorption.”

V. “The ‘801 patent” refers to U.S. Patent No. 6,015,801, entitled “Method for Inhibiting Bone Resorption.”

W. “The ‘294 patent” refers to U.S. Patent No. 6,225,294 B1, entitled “Method for Inhibiting Bone Resorption.”

X. The term “patents-in-suit” refers to the ‘077, ‘941, ‘590, ‘726, ‘410, ‘801, ‘329, ‘294, and ‘207 patents.

Y. The term “Abbreviated New Drug Applications” refers to an Abbreviated New Drug Application filed with the Food and Drug Administration.

Z. “FDA ” refers to the United States Food and Drug Administration.

AA. “Prior art” solely for the purpose of Merck’s requests shall mean any publication or activity predating the applicable date of filing for each of the patents-in-suit dealing with alendronate or any other pharmaceutically active biphosphonates and including but not limited to any publication or activity falling within 35 U.S.C. § 102 with respect to any of the patents-in-suit.

BB. The term “alendronate” means 4-amino-1-hydroxybutane-1,1-biphosphonic acid, any analog, and includes its monosodium acid salt form.

CC. A document or communication “relating to,” “related to,” or “concerning” a given subject means all documents or communications that constitute, contain, embody, comprise, reflect, identify, state, refer to, deal with, comment on, mention, respond to, describe, involve, or are in any way pertinent to that subject, including, but not limited to, documents concerning the presentation of other documents.

DD. “Any” or “each” should be understood to include and encompass “all”; “or” should be understood to include and encompass “and”; and “and” should be understood to include and encompass “or”.

EE. The use of the singular form of any word includes the plural and vice versa.

FF. For purposes of these requests, terms not specifically defined shall be given their ordinary meaning. Should Defendant be unable to understand the meaning of any term Defendant is invited to immediately seek its clarification through Merck's counsel.

REQUESTS FOR PRODUCTION

DOCUMENT REQUEST NO. 1

All opinions, legal or otherwise, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other affirmative defense.

DOCUMENT REQUEST NO. 2

All documents and things, including correspondence with counsel, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other affirmative defense.

DOCUMENT REQUEST NO. 3

All documents and things relating to patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of any of the patents-in-suit.

DOCUMENT REQUEST NO. 4

All opinions, legal or otherwise, relating to the validity of the patent term extension or the patent term restoration of the '077 patent.

DOCUMENT REQUEST NO. 5

All documents and things, including correspondence with counsel, relating to validity of the patent term extension or the patent term restoration of the '077 patent to Defendant.

DOCUMENT REQUEST NO. 6

All documents and things relating to any policies or practices of Defendant concerning patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of the patents of others.

DOCUMENT REQUEST NO. 7

All Abbreviated New Drug Applications filed by Defendant with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 8

All supplements and amendments to Abbreviated New Drug Applications filed by Defendant with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 9

All documents and things relating to or constituting correspondence or other communications, including but not limited to draft documents and correspondence, among Defendant and/or between Defendant and/or any other person and any foreign or domestic regulatory agency including, but not limited to, the FDA or a foreign counterpart concerning alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 10

All documents and things relating to the patent certifications made by Defendant as part of an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 11

All documents and things relating to Defendant's decision to file an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active

biphosphonate formulations, including, but not limited to, the timing of the filing, the cost for the filing, and any cost or benefit analysis.

DOCUMENT REQUEST NO. 12

All documents and things relating to the timing, schedule, timetable or projection of approval of Defendant's Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 13

All documents and things relating to any labeling, promotion, advertising or claims by Defendant for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S or any other country.

DOCUMENT REQUEST NO. 14

All documents and things relating to Defendant's decision for file a patent certification as part of an Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulation.

DOCUMENT REQUEST NO. 15

All documents and things relating to FDA notification of "tentative approval" of the Abbreviated New Drug Application for Defendant's alendronate formulations.

DOCUMENT REQUEST NO. 16

All documents and things relating to the patents-in-suit.

DOCUMENT REQUEST NO. 17

All documents and things relating to the first awareness of the patents-in-suit by Defendant.

DOCUMENT REQUEST NO. 18

All documents and things created before the filing of this suit concerning or constituting any prior art search relating to any of the patents-in-suit.

DOCUMENT REQUEST NO. 19

All prior art that Defendant contend supports an allegation that any claim of the patents-in-suit is invalid.

DOCUMENT REQUEST NO. 20

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are not, and/or will not be, infringed by Defendant.

DOCUMENT REQUEST NO. 21

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are unenforceable.

DOCUMENT REQUEST NO. 22

All documents and things forming the basis of, or relating to, any and all defenses pleaded by Defendant that any claim of the patents-in-suit is invalid.

DOCUMENT REQUEST NO. 23

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as lacking a written description.

DOCUMENT REQUEST NO. 24

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as the specification does not enable the claims.

DOCUMENT REQUEST NO. 25

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as indefinite.

DOCUMENT REQUEST NO. 26

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as lacking utility.

DOCUMENT REQUEST NO. 27

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are anticipated by the prior art.

DOCUMENT REQUEST NO. 28

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as obvious in light of the prior art.

DOCUMENT REQUEST NO. 29

All documents and things relating to the April 21, 1997 patent term restoration of the '077 patent under 35 U.S.C. § 156.

DOCUMENT REQUEST NO. 30

All documents related to Defendant's patent certification and Notice of Patent Certification for Abbreviated New Drug Applications for alendronate formulations.

DOCUMENT REQUEST NO. 31

All documents and things relating to any legal or administrative proceedings concerning the manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active bisphosphonate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 32

All documents and things concerning any indemnification and/or insurance provided to, received, or granted by Defendant against or for the infringement of any of the patents-in-suit.

DOCUMENT REQUEST NO. 33

All documents and things relating to Defendant's production or attempted production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 34

All documents relating to research and development of manufacturing processes for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 35

All documents and things relating to or comprising communications among Defendant and/or between Defendant and any other person concerning the design, development, testing, structure, function and/or operation of manufacturing facilities for the production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 36

All documents and things relating to U.S. or foreign lawsuits, pending or previously resolved, or investigations regarding Defendant's production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 37

All documents and things relating to any manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active biphosphonate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 38

All documents and things relating to any supply agreement for alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 39

All documents and things constituting or relating to negotiations between Defendant and suppliers or potential suppliers of alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 40

All documents and things relating to any desire, consideration or need by Defendant to obtain or not obtain a license under any of the patents-in-suit.

DOCUMENT REQUEST NO. 41

All documents and things constituting or relating to licenses and/or agreements for alendronate or any other pharmaceutically active biphosphonate among Defendant and/or between Defendant and any other person.

DOCUMENT REQUEST NO. 42

All documents and things related to licensing agreements among Defendant and/or between Defendant and any other person for the production, distribution or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 43

All documents and things concerning marketing or whether to market alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 44

All documents and things relating to market share and market potential for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 45

All documents and things relating to the dollar amounts expended by Defendant or any other person for the promotion of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 46

All documents and things relating to all forms of promotions for or marketing of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country by Defendant or any other person.

DOCUMENT REQUEST NO. 47

All documents and things created after January 1, 1993, relating to any market survey, market analysis, sales projections or forecast of customer demand with respect to alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 48

All documents and things relating to any communications to or from Defendant's sales forces, agents, dealers, representatives, distributors, the press, or any news wire service relating to this lawsuit, and/or any of the patents-in-suit.

DOCUMENT REQUEST NO. 49

All documents and things relating to research and development of alendronate and alendronate formulations or any other pharmaceutically active biphosphonate and its formulations.

DOCUMENT REQUEST NO. 50

Two hundred alendronate tablets for each dosage form produced by Defendant for the purpose of obtaining FDA approval.

DOCUMENT REQUEST NO. 51

All documents and things relating to any tests comparing Merck's alendronate product with the alendronate product that Defendant produced.

DOCUMENT REQUEST NO. 52

Any samples of Merck products that contain alendronate or any other pharmaceutically active biphosphonate that have been tested or examined by Defendant or any persons working on their behalf.

DOCUMENT REQUEST NO. 53

All documents and things relating to any testing performed using Merck's alendronate product.

DOCUMENT REQUEST NO. 54

All documents and things relating to Defendant's knowledge of Merck's activities in the research, patenting, development, manufacture, use or sale of any pharmaceutical formulation of alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 55

All documents and things Defendant contemplate introducing at trial.

DOCUMENT REQUEST NO. 56

All documents and/or things relating to any experts Defendant contemplate calling at trial, including but not limited to the educational and technical training of each expert and any publications authored by such expert.

DOCUMENT REQUEST NO. 57

All documents and things, including but not limited to organizational charts, showing identity and job titles of employees since January 1, 1993 to the present for all of Defendant's divisions and/or subsidiaries involved in the research, development, production, design, manufacture or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 58

All documents and things setting forth Defendant's document retention and/or destruction policies.

DOCUMENT REQUEST NO. 59

All documents and things relating to or constituting applications by Defendant to obtain regulatory approval for alendronate or any other pharmaceutically active biphosphonate in a foreign country.

DOCUMENT REQUEST NO. 60

Two grams of each ingredient in the alendronate tablets produced by Defendant for the purpose of obtaining FDA approval.

MORRIS, NICHOLS, ARSHT & TUNNELL



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March 19, 2002

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CERTIFICATE OF SERVICE

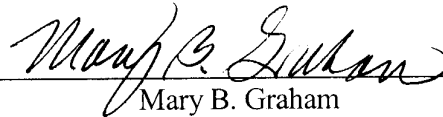
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Re: *Merck v. Teva*

Dear Nick:

I have Jason Abair's letter dated December 10, 2002.

As discussed yesterday, I confirm that Teva has conducted a diligent search for documents responsive to Merck's document requests for all persons at Teva involved with the development of Teva's weekly alendronate sodium after the complaint in this action was filed and again after Merck served its document requests on Teva.

I also confirm that Teva agrees to exchange its source log with Merck on Friday, December 13, 2002.

As we have now complied with your requests, we expect that Merck will withdraw its motion to compel today.

Sincerely,

A handwritten signature in black ink, appearing to read 'MLP', written over a horizontal line.

Maria Luisa Palmese

cc: Jason C. Abair, Esq. (via facsimile)

REDACTED

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

MERCK & CO., INC.,)	
)	
Plaintiff,)	
)	
v.)	Civil Action No. 01-048 (JJF)
)	(Consolidated)
TEVA PHARMACEUTICALS USA, INC.,)	
)	
Defendant.)	

**TEVA PHARMACEUTICALS USA, INC.'S
POST-TRIAL BRIEF**

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March 28, 2003

**NON – CONFIDENTIAL VERSION
AS AGREED BY PARTIES**

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INTRODUCTION

In October 1995, Merck launched its first alendronate sodium (“alendronate”) products. The dosage strengths were 10 mg daily for treatment of osteoporosis and 40 mg daily for treatment of Paget’s disease. Just six months later, in April 1996, a publication called *Lunar News* disclosed the once-weekly oral administration of alendronate at a higher dose to manage osteoporosis. Three months later, in July 1996, *Lunar News* again disclosed once-weekly administration of alendronate to manage osteoporosis, and this time it suggested specific dosage strengths.

A year later, in July 1997, more than a year after *Lunar News* had twice disclosed the concept, Merck filed a patent application directed to once-weekly administration of alendronate for, *inter alia*, the management of osteoporosis. Merck’s patent application issued as U.S. Patent No. 5,994,329 (the “’329 patent”), the patent in suit here, the only asserted claims of which claim the once-weekly administration of alendronate to treat and prevent osteoporosis.

For the reasons set forth herein, the Court should find the asserted claims of the ’329 patent invalid under 35 U.S.C. §§ 102 and 103 as anticipated by and as obvious in view of the *Lunar News* disclosures. Merck’s only response to those disclosures is to argue that no person of skill in the art would have believed and followed the *Lunar News* teachings because of a fear that increased gastrointestinal side effects would accompany higher once-weekly doses of alendronate. The evidence at trial, however, showed that this “fear defense” is baseless, and that Merck concocted it solely for purposes of litigation.

This case does not represent the first time the patentability of Merck’s invention has been litigated. In *Teva Pharmaceuticals Ltd et al. v. Istituto Gentili SpA et al.* (High

Court of Justice, Chancery Division, Patents Court, January 22, 2003), the British High Court held invalid Merck's European patent that corresponds to the '329 patent. That patent claimed the invention defined by claim 23 of the '329 patent: the weekly administration of 70 mg alendronate sodium to treat osteoporosis. In finding that patent invalid, the British Court specifically rejected the "fear defense" on which Merck relies here. (DTX405)

The Court should also find the '329 patent unenforceable. The evidence at trial showed that Merck's principal inventor had a copy of the July 1996 *Lunar News* before he filed his patent application, and was twice specifically directed to the relevant passages, but failed to disclose the reference to the PTO. Merck's position that the inventor did not read the references until after this lawsuit was underway is not credible, and the Court should find that the inventor acted with intent to deceive the PTO. This inequitable conduct renders the patent unenforceable.

NATURE AND STAGE OF THE PROCEEDINGS

This case arises from the filing by Teva of supplements to its Abbreviated New Drug Application ("ANDA") for approval to market generic versions of Merck's once-weekly 70 mg and 35 mg products, which are approved for treatment and prevention of osteoporosis, respectively. As part of its supplements Teva included "paragraph IV" certifications directed to the patents Merck had listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") as covering Fosamax or its use (21 U.S.C. §355(j)(2)(A)(vii)(IV)). Initially, Teva filed paragraph IV certifications with respect to several patents listed by Merck in the Orange Book for 70 mg once-weekly Fosamax. When Merck later added U.S. Patent

6,225,294 to its Orange Book listing, Teva filed a paragraph IV certification against it. Later, Teva certified against all the patents Merck had listed for the 35 mg once-weekly product.

Because Teva was required to file paragraph IV certifications at different times, Merck filed three separate complaints, each within the 45-day period permitted by statute. (Civil Action Nos. 01-048 (JJF), 01-675 (JJF) and 01-728 (JJF)). Each of Merck's complaints alleges that Teva's ANDA filing was an act of infringement under 35 U.S.C. § 271(e)(2)(A), which defines filing an application for approval to market a drug covered by or whose use is covered by a patent listed in the Orange Book as an act of infringement. The three cases were later consolidated for all purposes as Civil Action No. 01-048 (JJF).

Merck has dismissed its claims relating to all originally asserted patents and claims except claims 23 and 37 of the '329 patent and claim 1 of U.S. Patent 4,621,077 (the "'077 patent"). The '077 patent was the subject of this Court's judgment entered December 2, 2002, the appeal from which is pending. The parties have agreed to be bound in this case by the outcome of that appeal, and the issues relating to the '077 patent were therefore not addressed at trial. (D.I. 128).

Finally, Teva has stipulated that if claims 23 and 37 of the '329 patent are valid, the commercial marketing of its proposed 70 mg and 35 mg alendronate sodium products would infringe those claims. Thus, the only issues to be addressed by the Court are the validity and enforceability of those two claims.

On February 11, 2003, Teva filed in this Court a "Motion to Preclude Plaintiff Merck & Co., Inc., From Relitigating the Factual Findings Underlying the Decision in *Teva Pharmaceuticals Ltd et al. v. Istituto Gentili SpA et al.*, (High Court of Justice,

Chancery Division, Patents Court, January 22, 2003).” Briefing on that motion was completed immediately prior to trial. For the reasons set forth in Teva’s supporting papers, Merck is bound by the factual findings of the British court, many of which are directly applicable to this case.

SUMMARY OF THE ARGUMENT

Claims 23 and 37 of the ’329 patent are invalid. Those claims define a method of treatment (claim 23) and prevention (claim 37) of osteoporosis comprising administering alenronate to a patient at a once-weekly dose of 70 mg and 35 mg respectively.

The July 1996 issue of *Lunar News* discloses every element of these claims to a person skilled in the art. That publication, which is prior art under 35 U.S.C. § 102(a), anticipates both claims.

Even if not anticipated, the claimed invention would have been obvious. The July 1996 *Lunar News* and the immediately preceding issue, published in April 1996, both teach once-weekly administration of alendronate for treatment and prevention of osteoporosis. A person skilled in the art would have motivated by the known problems associated with the administration of alendronate to employ the method taught by the *Lunar News*, and would have understood that the dosing regimen taught by the *Lunar News* would be safe and effective. The person of skill in the art would also have understood that the appropriate dosage strength for once-weekly dosing to be 70 mg for treatment and 35 mg for prevention of osteoporosis.

Merck’s principal defense to the *Lunar News* teachings is its litigation-inspired theory that a person skilled in the art would have been deterred from following those teachings because of a fear that doing so would cause increased incidence and severity of

gastrointestinal side effects. The evidence at trial demonstrated that Merck's "fear defense" is baseless, and should be rejected.

Merck's principal inventor, Dr. Yates, was twice directed to the July 1996 *Lunar News*, but never disclosed it to the PTO, even though he recognizes that it is "material" as that term is used in the patent law. Dr. Yates's testimony that he never read the publication is not credible and should be rejected. The '329 patent is unenforceable for inequitable conduct.

STATEMENT OF FACTS

I. BONE BIOLOGY AND THE MECHANISM OF ACTION OF ALENDRONATE

At trial, Teva called as its principal expert witness Dr. R.G.G. Russell, one of the world's leading experts in bone disease, and a pioneer in the use of bisphosphonates to treat osteoporosis. (DTX392). As Dr. Russell explained, bone is the tissue that provides mechanical support to the body. It is made up of a protein matrix, which is overlaid with mineral to give it hardness. Two principal types of cells maintain bone: (1) osteoclasts, which break down bone, and (2) osteoblasts, which build new bone. (Russell 108-09; DTX523 at 2).¹ The process of bone destruction and rebuilding is known as bone "remodeling." In bone remodeling process, osteoclasts attach to the bone surface, become activated, and erode away the bone material beneath them, leaving defects in the bone structure. The destruction of bone by osteoclasts is called bone "resorption." Osteoblasts then attach to the eroded surface of these defects, lay down new bone, and

¹ Trial testimony is cited herein by witness name and transcript page number. Deposition testimony is cited as "[witness name] dep. ____." Merck trial exhibits are cited "PTX____," and Teva trial exhibits are cited "DTX____."

then become quiescent. In the normal healthy adult the remodeling process is balanced, i.e., bone is destroyed and built at the same rate. (Russell 109-10; DTX523 at 3- 4).

In osteoporosis, bone destruction and formation are no longer balanced and bone is destroyed faster than it is replaced. Osteoporosis therefore can lead to bone that is thinner, weaker, more fragile and porous. (Russell 110-15; DTX523 at 7, 8).

Osteoporosis is a serious, costly disease. Osteoporosis patients include those who have lost bone mass but have no other clinical signs; such patients are diagnosed with laboratory tests such as x-rays or bone density measurements. Other osteoporosis patients may be diagnosed only after suffering a wrist or hip fracture. Osteoporosis of the spine and the resulting fractures of vertebrae, results in stooping or bending and loss of height. In frail patients, hip fractures resulting from osteoporosis may be disabling, leading to a diminished quality of life. Hip fractures leave some patients bedridden, and can lead to increased mortality. (Russell 111-12, 115-16).

Osteoporosis is treated primarily by inhibiting bone resorption — thus restoring the balance between bone destruction and bone formation. Alendronate inhibits bone resorption by blocking the bone destroying effects of osteoclasts. (Russell 116-17). A small portion of the ingested drug makes its way to and adheres to the bone surface, where it resides until it is taken up by osteoclasts. The alendronate then inhibits the osteoclasts from resorbing bone. This process was well understood when Merck filed the '329 patent application in July 1997. (Russell 121-22; DTX523 at 10).

Paget's disease is a common bone disease characterized by increased bone resorption. In Paget's disease, increased bone remodeling occurs in localized areas of the skeleton. Patients with Paget's disease also exhibit a spectrum of clinical problems, but Paget's disease is often diagnosed in patients without symptoms during routine blood

tests or x-ray examinations, and treatment is often encouraged even for these asymptomatic patients. (Russell 96-98; DTX531 at 72). Depending on the site of involvement, if Paget's disease is not detected and treated early it can lead to increases in bone size, fractures, and deformity, potentially resulting in other complications. (Russell 97). Like osteoporosis, Paget's disease is treated by inhibiting bone resorption with alendronate. (Russell 125-26).

II. MERCK'S ONCE-DAILY ALENDRONATE PRODUCTS

Merck launched its daily Fosamax products in October 1995, about 21 months before filing the application for the '329 patent. Merck initially offered two daily dosage forms: a 10 mg tablet to treat osteoporosis, and a 40 mg tablet to treat Paget's disease. Early in 1997, Merck began to market a 5 mg daily tablet for prevention of osteoporosis. (Russell 125-27; DTX346).

The biological characteristics of alendronate required patients to follow a set of complicated and inconvenient dosing instructions. Because alendronate would be bound up by metal ions (e.g., calcium) in food and beverages, Merck instructed patients to take the product upon arising in the morning, with plain water, a half hour before eating. Because alendronate was recognized to be a potential irritant to the esophagus, patients were instructed to take the product with a full glass of water and to sit or stand upright for at least a half hour after taking the medication. The latter instruction was designed to ensure that the tablets would enter the stomach efficiently, without being held up in the esophagus where they could cause irritation. Patients, especially the very elderly, found these instructions to be inconvenient and difficult to adhere to on a daily basis, sometimes to the point where they stopped taking the medication. (Russell 126-28).

III. THE '329 PATENT

The '329 patent issued November 30, 1999, based on U.S. provisional applications filed July 22 and July 23, 1997. (DTX1). Merck has stipulated that it will not assert an invention date for the asserted claims of the '329 patent before July 22, 1997. (D.I. 128).

The '329 patent discloses less-frequent-than-daily administration of bisphosphonates (e.g., alendronate) to inhibit bone resorption. Claims 23 and 37, the only asserted claims, relate specifically to treatment and prevention of osteoporosis by once-weekly administration of alendronate. These claims are dependent from several others and are summarized as follows:

23. A method for treating osteoporosis in a human comprising orally administering about 70 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.
37. A method for preventing osteoporosis in a human comprising orally administering about 35 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.²

The idea behind the asserted claims is simple. Instead of taking 10 mg or 5 mg of alendronate every day to treat and prevent osteoporosis, take seven times that amount once per week. The only difference between the claimed regimen and the prior regimen is the frequency of administration and the strength of the dose. Although the asserted claims relate to the management of osteoporosis in humans, the '329 patent includes no data derived from the administration of alendronate to humans at all, and no data or

² Although Merck has made gastrointestinal side effects the centerpiece of this case, nothing in the language of either asserted claim relates in any way to such side effects or their minimization.

examples demonstrating the efficacy of the claimed methods at treating or preventing osteoporosis in any species. (Russell 124-25; Yates 547-48).

The '329 patent specification recognizes that the inconvenience of the alendronate dosing regimen provides a motivation to administer the drug less frequently, and proposes the invention as a solution to that problem:

[B]ecause bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

(DTX1, col. 2, line 67-col. 3, line 6);

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing.

(DTX1, col. 4, lines 14-19).

Although the '329 patent contains no clinical data, the specification states without qualification that the disclosed invention surprisingly results in fewer adverse gastrointestinal side effects:

[T]he administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes *less* adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency.

(DTX 1 at col. 3, line 64-col. 4, line 2) (emphasis added). At trial, Merck presented no clinical evidence supporting this assertion. In fact, there is no evidence that the weekly administration of alendronate provides a clinically significant safety advantage compared to its daily administration (Russell 198-99), and Dr. Arthur Santora, an inventor on the '329 patent, testified that Merck has never conducted a study that could demonstrate such an advantage. (Santora dep. 295-97).

IV. THE SCOPE AND CONTENT OF THE PRIOR ART

Just six months after the release of Merck's daily alendronate product, and well before Merck's alleged invention date of July 22, 1997, a publication called *Lunar News* disclosed the once-weekly administration of alendronate for management of osteoporosis. *Lunar News* was a periodical distributed approximately quarterly by Lunar Corporation, a company that manufactures and markets "bone densitometers." (Russell 128-29). Bone densitometers — devices that measure the amount of bone a patient has — form the basis for the diagnosis and clinical management of many osteoporosis patients. (Russell 129-30).

Lunar Corporation was founded and led by Dr. Richard Mazess, a Professor Emeritus at the University of Wisconsin. Dr. Mazess has a Ph.D. in physical anthropology and a research background in medical physics, physiology, and bone disease. In 1996, Lunar Corporation and Dr. Mazess were recognized leaders in bone densitometry. Dr. Mazess developed some of the first bone densitometers and is credited with making bone densitometry available for widespread use in the management of osteoporosis. (Russell 131-32, 227-28; Mazess dep. 30-31, 33-35, 43, 50-56). In 1996 Dr. Mazess was President and CEO of Lunar, and was the author of the articles appearing in *Lunar News*. (Mazess dep. 55-56).

Each issue of the *Lunar News* was widely distributed. (Mazess dep. 57). Both Teva's bone expert, Dr. Russell, and Merck's expert, Dr. Papapoulos, testified that they received the *Lunar News*, and copies were received at and circulated within Merck, including to Dr. Yates, the principle inventor of the '329 patent. (DTX38; Russell 132-33; Papapoulos 662-63). The *Lunar News* included review articles on various topics

related to bone disease and osteoporosis. (Russell 129). The publication provided exhaustive reviews of the pertinent literature, and the bibliographies of each issue included hundreds of articles. (See DTX417 at 34-44; DTX418 at 27-36). Both Dr. Russell and Merck's expert Dr. Papapoulos testified that the *Lunar News* was a valuable resource in terms of providing current references in the pre-internet era. (Russell 133; Papapoulos 687). Merck's Dr. Santora characterized the *Lunar News* as a "nice exhaustive summary of the literature." (Santora dep. 39).

A. April 1996 *Lunar News*

In a section entitled "Update: Bisphosphonate," the April 1996 edition of the *Lunar News* discloses once-weekly dosing of alendronate. The article discusses the difficulties of the dosing regimen, and then proposes once-weekly dosing of alendronate as a solution:

One of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is bioavailable. Even coffee or juice reduces this by 60%, and a meal reduces it by >85%. Alendronate must be taken, after an overnight fast, 30-60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly to maintain chronically. *An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested.*

(DTX417 at 31) (citations omitted) (emphasis added).

The evidence at trial, including the testimony of Merck's expert, showed that a person of skill in the art in 1996 reading this passage and following the direction to administer alendronate once-weekly would have understood that the appropriate weekly doses should be 70 mg for treatment of osteoporosis and 35 mg for prevention. (Russell 149-50, 152-53; Papapoulos 682, 684). Moreover, the evidence showed that the phrase "needs to be tested" would have been understood to mean that the regimen should be

examined in a clinical trial so that it could be approved for use in patients. Teva's expert, Dr. Russell, testified that such clinical trial testing is a step that must be carried out for every drug, regardless of the state of knowledge or any expectation of success beforehand. (Russell 151-52).

B. July 1996 *Lunar News*

In July 1996, Lunar published another issue of the *Lunar News* disclosing weekly dosing of alendronate. The July 1996 *Lunar News* discussed the problem of the inconvenience of the alendronate dosing regimen, and again presented once-weekly dosing as a solution:

The limited bioavailability of alendronate (0.8%) requires that it be taken on an empty stomach upon awakening with a full glass of water (not tea, coffee, or juice), and the patient must remain upright for 30 to 60 minutes. A few elderly women can tolerate this regime for a only [sic] week or two.

* * *

The difficulties with oral bisphosphonates may favor their episodic (once/week), or cyclical (one week each month) administration. *Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.*

(DTX418 at 23 (citations omitted) (emphasis added)).

The principal addition to the prior disclosure was the suggestion of specific dosage strengths: 40 mg and 80 mg once per week. The 40 mg and 80 mg dosages recited in the July 1996 *Lunar News* were based on the commercial availability of a 40 mg tablet, which Merck was marketing in 1996 for the treatment of Paget's disease. (Russell 141-42).

C. In July 1997 Persons of Skill In the Art Would Have Expected Once-Weekly Dosing To Be Effective To Treat Osteoporosis and Would Have Known that the Weekly Dose Should Be About Seven Times the Daily Dose

In addition to the *Lunar News* disclosures discussed above, which specifically taught once-weekly dosing of alendronate, the prior art demonstrated that teaching to be soundly based on well-understood scientific principles and data reported in the technical literature. Further, this same literature not only taught that once-weekly dosing would be effective, but taught the size of that effective dose.

Alendronate is taken up by bone, and it resides in bone for a long time. Ten years after taking a dose of alendronate, approximately one-half of the alendronate initially attaching to bone will remain. (Russell 119). This characteristic of the compound affects how it behaves in a patient's body over time. It is not disputed that in July 1997, a person of ordinary skill in the art would have expected the weekly administration of alendronate at seven times the daily dose to be as effective in treating osteoporosis as daily administration. (Russell 144; Papapoulos 670-71; Yates 548-49). This expectation was based on pre-clinical studies, which show that doses of alendronate administered weekly, twice-weekly, or even every two weeks were effective in inhibiting bone resorption. (Russell 144-46; *see also* DTX80, 82, 396, 398, 399).

One of these studies, by Seedor *et al.*, also demonstrated that the total dose of alendronate administered over time, and not the frequency of dosing, determines alendronate's effect on bone resorption. In terms of the asserted '329 patent claims, based on this study a person of skill in the art would have expected the effect of 70 mg or

35 mg weekly to be the same as 10 mg or 5 mg administered every day, respectively. (Russell 146-53; DTX80).

Moreover, it was known in July 1997 that the amount of alendronate absorbed from a dose was linear between 5 mg and 80 mg. (Russell 147-48; DTX3 at 15). Because of this linearity of absorption, a person skilled in the art would have expected the same amount of alendronate to be absorbed whether taken on a daily or weekly basis, as long as the total amounts were the same. (Russell 147-48).

D. In July 1997 A Person Of Skill in the Art Would Have Expected Once-Weekly Dosing of Alendronate to Exhibit Tolerability Similar to That of Once-Daily Dosing

The evidence demonstrates that no deterrent existed in the prior art to discourage a person of ordinary skill in the art from following the teachings of the April and July 1996 Lunar News and administering alendronate once-weekly at about seven times the daily dose. (Russell 154-55). The evidence shows that (1) Merck's 10 mg daily alendronate product was well-tolerated in Merck's very large clinical trials and in clinical practice, (2) 40 mg of alendronate *daily* was well-tolerated in clinical trials and clinical practice, and (3) even 80 mg of alendronate *daily* (i.e., 560 mg per week – eight times the claimed weekly dose) was well-tolerated in clinical trials. This clinical trial information and clinical experience, considered as a whole, would have led the person of ordinary skill in the art to expect that a weekly dose of 70 mg alendronate would be well-tolerated.

1. Merck's Clinical Trials and Clinical Experience Showed that 10 mg Alendronate Daily Was Well-Tolerated

Before approving alendronate, the FDA required Merck to perform clinical trials large enough to demonstrate that Fosamax was effective at preventing osteoporotic fractures. (Russell 158). This requirement necessitated the treatment of many patients over an extended period. Dr. Laurence Hirsch, Merck's Executive Director for Clinical

Research, and the scientist supervising the '329 patent inventors in 1995-96, called the Fosamax trials "the largest and most accelerated program" Merck had ever done. (DTX312 at 16-17; Hirsch dep. 22, 34-35). He characterized the Fosamax clinical program as "unparalleled in terms of actual patient years of exposure in controlled clinical trials." (DTX312 at 17; Hirsch dep. 36-37). All these clinical trials, which were carried out and reported in the literature before July 1997, demonstrated that daily Fosamax was well tolerated in osteoporosis patients, and that no statistically significant difference existed in the frequency or severity of upper gastrointestinal adverse events between alendronate and placebo. (Russell 169).

Upper gastrointestinal symptoms include nausea, gastric (i.e., stomach) pain, dyspepsia (i.e., stomach upset), heartburn, and abdominal distension. These mild symptoms are common in the general population and are especially common in the population of people that would ordinarily take Fosamax. In fact, ten to 40 percent of the osteoporosis population experience these symptoms whether taking medication or not. (Russell 156-57). Dr. Louis Sherwood, Merck's Senior Vice President for U.S. Medical and Scientific Affairs in 1996-97, testified that Merck's clinical trials had demonstrated that 20-25 percent of older women given a placebo (i.e., a tablet without alendronate in it) have gastrointestinal side effects. (Sherwood dep. 6, 192-93).

In Merck's clinical trials, the rates of gastrointestinal side effects in patients taking 10 mg alendronate daily could not be distinguished from the rates seen in patients taking placebo. In 1995, Liberman *et al.* reported on a Merck-sponsored clinical trial involving almost 900 women and daily alendronate doses up to 20 mg. The authors concluded that alendronate was "well tolerated," and that no difference in adverse effects could be detected between alendronate and placebo. (DTX276; Russell 160-61).

Reporting on a related trial involving approximately 500 women, Devogelaer stated in 1995 that a similar incidence of “drug-related” adverse events was seen in alendronate- and placebo-treated patients. (DTX401 at 147; Russell 165-66). In another Merck study, the Fracture Intervention Trial (“FIT”), more than 2000 patients were treated with either alendronate or placebo. (DTX341). A 1996 report on the FIT stated that no difference could be discerned between the alendronate- and placebo-treated groups for any category of upper gastrointestinal adverse events. Significantly, the authors reported that forty percent of women taking placebo complained of upper gastrointestinal problems. (DTX341 at 1539; Russell 167-68).

These results, demonstrating that daily alendronate was well tolerated and had a side effect profile indistinguishable from placebo in clinical trials, were repeatedly touted by Merck scientists, including Dr. Yates, at scientific meetings following the launch of Fosamax in 1995. (Russell 169-70). Indeed, Dr. Yates reported the tolerability of daily administration of 10 mg alendronate in Merck’s clinical trials to be “remarkably similar” to placebo. (Yates 560). Moreover, before this litigation began he wrote that actual post-marketing clinical experience with alendronate was remarkably consistent with the results of Merck’s clinical trials:

[O]n closer inspection, there is a remarkable consistency between the upper GI safety data from placebo-controlled alendronate clinical trials of postmenopausal osteoporosis treatment and the range of experience in clinical practice.

(DTX272 at 2; *see* Yates 563).

2. Merck’s Trials and Clinical Experience Demonstrated That 40 mg *Daily* was Well-tolerated

Merck’s clinical trials also demonstrated that patients easily tolerated the 40 mg alendronate daily dose. In 1993, Harris reported on a study involving the use of placebo,

5 mg, 20 mg, or 40 mg Fosamax daily. He concluded that “[a]lendronate was well tolerated over the entire dose range.” (DTX 340 at 1403; Russell 170-71). In 1995, Chesnut reported the results of a study in post-menopausal osteoporotic women treated with placebo, 5 mg, 10 mg, 20 mg and 40 mg daily in various combinations over a three-year period. (DTX14). Chesnut reported that seven of 63 patients taking the 40 mg daily dose withdrew from treatment because of gastrointestinal side effects, although none of these side effects was serious. (DTX14 at 150; Russell 183-84). Thus, Chesnut demonstrated that approximately 90 percent of post-menopausal osteoporotic patients had no difficulty tolerating the 40 mg daily dose. (Russell 184-85; *see also* DTX192 at 8).

In 1996, Dr. Ethel Siris (and Merck’s Dr. Yates) reported a study comparing the administration of 40 mg of alendronate daily to etidronate for the treatment of Paget’s disease. Drs. Siris and Yates concluded that 40 mg alendronate daily was “well tolerated and had a safety profile similar to that of etidronate.” (DTX271; Russell 175). Similarly, in 1996 Dr. Reid (again with Dr. Yates) reported the results of a study in Paget’s patients treated with either 40 mg of alendronate or placebo daily. (DTX15). Drs. Reid and Yates reported that the administration of 40 mg of alendronate daily was “well tolerated” and that there was no difference between alendronate and placebo in terms of adverse experiences. (Russell 178; DTX15 at 345).

The actual clinical experience with 40 mg alendronate daily after the product was marketed conforms to the reported clinical trial experience. By March of 1996, just five months after Fosamax was launched in the U.S., 5000 patients had received the 40 mg daily dose of alendronate for Paget’s disease. (DTX6 at 1018). There is no evidence that the thousands of patients taking this dose experienced any greater degree of gastrointestinal side effects, even though the dose is four times the daily dose used for

osteoporosis and four times the “about 70 mg” weekly dose recited in claim 23. (Russell 172-73; *see also* DTX521 at 6).

3. 80 mg Alendronate *Daily* Was Shown to be Well-Tolerated

Prior to July 1997, studies had shown that even higher daily doses of alendronate were well tolerated. In 1997, Khan *et al.* published the results of a study comparing 40 mg alendronate daily with 80 mg alendronate daily in the treatment of Paget’s disease. (DTX342). Khan reported that there was “no apparent dose response” between 40 mg daily and 80 mg daily in terms of gastrointestinal side effects, and Merck concluded from his data that the 80 mg dose was “well tolerated” (DTX 342 at 269; DTX192 at 8).

These studies show that patients dealt well with daily doses of alendronate from 10 mg to 80 mg. The data certainly support an expectation that patients would likewise deal well with a 70 mg dose that they took only once per week.

V. THE LEVEL OF ORDINARY SKILL IN THE ART

The ’329 patent is directed to scientists with an M.D. and/or Ph.D., or their equivalent, working in the field of and doing research on osteoporosis. Such a person would also be familiar with the publications and technical literature in the field of bisphosphonates and osteoporosis. (Russell 143-44).

VI. THE DIFFERENCES BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART

The prior art in this case spells out the claimed invention. No differences exist between it and the prior art. As discussed below, the July 1996 *Lunar News* anticipates claims 23 and 37. At a minimum, the background prior art discussed above teaches any differences between the *Lunar News* disclosures and the invention of claims 23 and 37.

The prior art laboratory, clinical trial and actual clinical experience available to persons of ordinary skill in the art in July 1997 disclosed once-weekly dosing of alendronate and the motivation for that regimen, taught the appropriate dose, taught that the dose would be effective, and provided assurance that the dose would be safe and well tolerated by patients.

ARGUMENT

I. THE JULY 1996 *LUNAR NEWS* ANTICIPATES CLAIMS 23 AND 37

A. The July 1996 *Lunar News* is Prior Art that Was Not Considered by the PTO Examiner

The July 1996 *Lunar News* was a printed publication. It was widely distributed, having a circulation among the relevant audience of about 20,000. (Mazess dep. 57). That particular issue was in the hands of Merck at least as early as September 1996. (DTX38). Since Merck has stipulated that it does not assert an invention date before July 22, 1997 (D.I. 128), the July 1996 *Lunar News* is prior art under 35 U.S.C. § 102(a).

Because a patent is presumed valid, 35 U.S.C. § 282, Teva has the burden of proving that the '329 patent claims are invalid by clear and convincing evidence. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). Teva's burden is more easily carried here, however, because Merck failed to provide the PTO with the July 1996 *Lunar News*. Indeed, despite the fact that Dr. Yates, the principal inventor, had twice been directed to the July 1996 *Lunar News*, neither Merck nor anyone on its behalf ever disclosed it to the PTO, and the examiner never uncovered it on his own. The fact that this prior art was not before the Examiner makes the presumption of validity associated with the '329 patent more easily overcome because no deference is due to the PTO with

respect to evidence that it did not consider. *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 714 (Fed. Cir. 1984) (“Deference is due the Patent and Trademark Office decision to issue the patent with respect to evidence bearing on validity which it considered but no such deference is due with respect to evidence it did not consider.”); *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 905 (Fed. Cir. 1985); *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1358-60 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 821 (1984).

B. The July 1996 *Lunar News* Anticipates Claims 23 and 37

To be patentable, an invention must be new. Under 35 U.S.C. § 102(a), a person is not entitled to a patent if the claimed invention was “... described in a printed publication” before the invention thereof. This requirement ensures that the public is not deprived of information that is already within the public domain. If the invention is not new, it is said to be anticipated. A prior art reference anticipates a claimed invention if it discloses every limitation of the claim, either expressly or inherently. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001); *Atlas Powder Co.*, 190 F.3d at 1346; *Ciba-Geigy Corp. v. Alza Corp.*, 864 F. Supp. 429, 434-35 (D.N.J. 1994), *aff’d in pertinent part*, 68 F.3d 487 (Fed. Cir. 1995). Anticipation is a question of fact. *In re Graves*, 69 F.3d 1147, 1151 (Fed. Cir. 1995).

1. The July 1996 *Lunar News*

The section of the July 1996 *Lunar News* entitled “Update: Bisphosphonate” discusses the use of bisphosphonates for managing osteoporosis. It describes bisphosphonates as a “. . . major focus for researchers dealing with osteoporosis,” and identifies “[a]lendronate (Fosamax by Merck)” as “the current leader among bisphosphonates in several countries.” (DTX418 at 23). The article continues, providing

an update on the use of bisphosphonates, and in discussing the well-known problems associated with oral alendronate therapy, suggests administering alendronate orally in “40 or 80 mg” doses once weekly rather than daily:

Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

(DTX418 at 23). This disclosure anticipates both claims 23 and 37.

2. The July 1996 *Lunar News* Expressly Discloses all Elements of Claims 23 and 37

Claim 23 defines a method of treating osteoporosis which comprises orally administering about 70 mg alendronate monosodium trihydrate, on an active alendronic acid basis, once-weekly. The July 1996 *Lunar News* expressly discloses each of these elements. It discusses the use of bisphosphonates, including alendronate, in “dealing with osteoporosis,” which means the treatment and prevention of osteoporosis. (Russell 137). The July 1996 *Lunar News* also specifies that the alendronate therapy it is discussing includes “oral” alendronate therapy, and that the term “alendronate” refers to “Fosamax by Merck.” The active ingredient of Fosamax was well known to be alendronate monosodium trihydrate, and the dosage strengths of Fosamax were known to be reported on an alendronic acid basis. (DTX394; Russell 138-39). The article then specifies that the drug can be administered on a weekly basis at a dose of 80 mg: “...oral alendronate potentially could be given in a 40 or 80 mg dose once/week.” (DTX418 at 23). The undisputed testimony at trial demonstrated that to a person skilled in the art, 80 mg alendronate once per week is clinically indistinguishable from 70 mg once a week, and is therefore “about 70 mg.” (Russell 138). Indeed, Merck itself viewed 80 mg and 70 mg as the same weekly dose. (DTX147 at MK0158265). The July 1996 *Lunar News* therefore discloses every element of claim 23: Treatment of osteoporosis by

oral administration of about 70 mg alendronate monosodium trihydrate on an alendronic acid basis once weekly.

Claim 37 claims a method for preventing osteoporosis in a human being comprising orally administering about 35 mg of alendronate sodium on an alendronic acid basis as a unit dosage according to a continuous schedule having a dosing interval of once-weekly. (DTX1). Thus, the only differences between the two claims are that claim 23 is directed to “treatment” of osteoporosis with a 70 mg weekly dose, and claim 37 is directed to “prevention” with a 35 mg weekly dose.

As discussed above, the July 1996 *Lunar News* deals with both treatment and prevention of osteoporosis with alendronate and discloses the use of a 40 mg once-weekly oral dose. Again, the undisputed testimony at trial demonstrated that to a person skilled in the art, 40 mg alendronate once per week is clinically indistinguishable from 35 mg once a week and therefore is “about 35 mg.” (Russell 140; DTX147 at MK0158265). The July 1996 *Lunar News* therefore discloses every element of claim 37: prevention of osteoporosis by oral administration of about 35 mg alendronate monosodium trihydrate on an alendronic acid basis once-weekly.

The following chart summarizes the application of the July 1996 *Lunar News* to the asserted claims, and demonstrates a one-to-one correspondence between the publication and each claim element.

Claim 23	Claim 37	July 1996 <i>Lunar News</i>
A method of treating osteoporosis in a human comprising	A method of preventing osteoporosis in a human comprising	The subject of the article is the use of bisphosphonates in " <i>dealing with osteoporosis</i> " in humans. (DTX418 at 23). Dealing with osteoporosis includes both prevention and treatment of osteoporosis. (Russell 140).
orally administering		"Even oral alendronate potentially could be given..." (DTX418 at 23; Russell 137).
about 70 mg	about 35 mg	"... in a 40 or 80 mg ..." (DTX418 at 23). Eighty milligrams is "about 70 mg" because for practical purposes the doses are the same, and clinically would have the same effect on patients. (Russell 137-38). Similarly, 40 mg is "about 35 mg". (Russell 140-41).
of alendronate monosodium trihydrate		The article identifies alendronate as " <i>Fosamax by Merck</i> ," the active ingredient of which is alendronate monosodium trihydrate. (DTX418 at 23; Russell 138).
on an alendronic acid basis		Fosamax dosage strengths are reported on an alendronic acid basis. (DTX393 at A45, DTX394 at 1).
as a unit dosage		"... dose ..." (DTX418 at 23; Russell 139).
according to a continuous schedule having a dosing interval of once-weekly		"... once/week ..." (DTX418 at 23; Russell 139).

Since the July 1996 *Lunar News* discloses every element of claims 23 and 37, the subject-matter claimed by them is not new and those claims are invalid under 35 U.S.C. § 102(a).

3. Merck's Fear Defense is Irrelevant to Anticipation

Merck's "fear defense" is irrelevant to anticipation. First, claims 23 and 37 do not require that the once-weekly administration of alendronate meet any standard of safety or tolerability. Even if they did, such a requirement would not avoid anticipation, because

the property of tolerability is inherent in the method disclosed in the prior art. (Papapoulos 670-71). *See In re Cruciferous Sprout Patent Litigation*, 301 F.3d 1343, 1349-50 (Fed. Cir. 2002); *Atlas Powder Co., supra*; and *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 775 (Fed. Cir. 1985).

Second, although, as discussed below, Merck's fear defense is a baseless, it has no bearing on the issue of anticipation in any event. The concept of "teaching away" from an invention is inapplicable to an anticipation analysis and the Court should not consider it. *Bristol-Myers Squibb Co.*, 246 F.3d at 1378; *Celeritas Technologies v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir.1998).

II. THE INVENTION OF CLAIMS 23 AND 37 WOULD HAVE BEEN OBVIOUS TO A PERSON OF SKILL IN THE ART IN JULY 1997

Claims 23 and 37 of the '329 patent are invalid if the claimed inventions would have been obvious to a person of ordinary skill in the art at the time the invention was made. 35 U.S.C. § 103(a).³ The invention date here is no earlier than July 22, 1997. (D.I. 128). Thus, the issue is whether the prior art, taken as a whole, provided some teaching, suggestion or incentive as of July 1997 that would have rendered the claimed invention obvious to a person of ordinary skill in the art. *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) (the test for obviousness is whether the prior art "would have rendered the claimed invention obvious to one of ordinary skill in the art"); *Brown and Williamson*

³ Section 103(a):

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124 (Fed. Cir. 2000); *In re Mayne*, 104 F.3d 1339, 1341 (Fed. Cir. 1997).

Under *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), an obviousness determination requires a court to make fact findings as to (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of skill in the art. *See also Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 716 (Fed. Cir. 1991); *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894 (Fed. Cir. 1984). The ultimate determination of obviousness is a question of law based on these underlying facts. *Graham*, 383 U.S. 1, 17-18 (1966); *In re Berg*, 320 F.3d 1310, 1312 (Fed. Cir. 2003); *Sibia Neurosciences, Inc. v. Cadus Pharmaceuticals Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000); *Akzo N.V. v. United States International Trade Comm'n*, 808 F.2d 1471, 1480 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987).

Of course, the statutory presumption of validity applies to obviousness just as it does to anticipation. As discussed above, however, because neither the April and July 1996 issues of *Lunar News* was before the examiner, no deference is due to the PTO with respect to them, and Teva's burden is more easily carried. At trial, Teva carried that burden, proving by clear and convincing evidence that the subject matter of claims 23 and 37 would have been obvious in view of the April and July 1996 *Lunar News* articles, when those references are viewed against the backdrop of what was known to those skilled in the art. Merck's answer to that prior art – that fear of increased GI side effects would have deterred a person of skill in the art from carrying out the teaching of the *Lunar News* articles – was cobbled together for this litigation.

A. The *Lunar News* Taught the Claimed Invention

Both the April and July 1996 editions of the *Lunar News* explicitly disclose the weekly administration of alendronate for osteoporosis. (See DTX417 at 31; DTX418 at 23). A person skilled in the art would have understood in July 1997 that the weekly dose for treatment and prevention of osteoporosis should be “about 70 mg,” and “about 35 mg” respectively, and these doses are explicitly set out in the July 1996 *Lunar News*. (Russell 137-40, 149-53).

Not only did the *Lunar News* disclose the concept of once-weekly dosing and provide the appropriate dose, a person of ordinary skill would have predicted the *Lunar News* teaching to be effective. The biological properties of alendronate were well known long before 1997, and pre-clinical studies had demonstrated to persons skilled in the art that alendronate would exhibit a sustained response on bone resorption without the need for daily dosing. (Yates 548-49). Thus, the parties’ experts and Merck’s inventor agreed that in July 1997 a person of ordinary skill in the art would have known that weekly dosing of alendronate would be effective to inhibit bone resorption and to manage osteoporosis. (Russell 144-45; Papapoulos 667-71; *see also* Yates 548-49). In addition, it was known that absorption of alendronate was linear at least up to 80 mg, so that a sevenfold increase in the dose would lead to a sevenfold increase in the amount of drug absorbed. (DTX3 at 15; Russell 147-48). Indeed, Merck’s expert, Dr. Papapoulos, conceded that a person following the April 1996 *Lunar News* would have used 70 mg and 35 mg doses. (Papapoulos 682-84). For this reason, the person of ordinary skill would have had at least a reasonable basis to believe that the proposed weekly regimen would be effective. That reasonable expectation is all the law requires. *In re Longi*, 759 F.2d

887, 897 (Fed. Cir. 1985); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986); *In re Lamberti*, 545 F.2d 747, 750 (C.C.P.A. 1976).

B. A Motivation Existed to Employ Once-Weekly Dosing

The dosing difficulties with alendronate were well known to persons skilled in the art. The patient was required to take the tablet before eating, to remain upright for a half an hour, and to take the tablet with a full glass of water. This regimen was highly inconvenient, and was responsible for some patients discontinuing treatment (Russell 128), and for others cutting corners and risking the consequences of improper dosing. Any dosing regimen that could reduce the inconvenience would have been welcomed.

Both the April and July 1996 editions of *Lunar News* explicitly state the motivation to administer alendronate weekly: to improve patient convenience and therefore compliance with the dosing instructions. (Russell 150, 154). Thus, the very prior art that taught the claimed invention also disclosed the motivation to make it. See *B.F. Goodrich Co. v. Aircraft Braking Systems Corp.*, 72 F.3d 1577, 1582-83 (Fed. Cir. 1996); *Nursery Supplies, Inc. v. Lerio Corp.*, 45 U.S.P.Q.2d 1332, 1334 (M.D. Pa. 1997); see also *Milliken Research Corp. v. Dan River, Inc.*, 739 F.2d 587, 602 (Fed. Cir. 1984); *In re Bozek*, 416 F.2d 1385, 1390 (C.C.P.A. 1969).

C. A Person of Skill in the Art Would Not Have Been Deterred From Once-Weekly Dosing Because of “Fear” of Increased GI Side Effects

At trial, Merck never contended that the *Lunar News* and the other prior art did not teach the claimed invention. Instead, Merck argued that a person of ordinary skill in the art would have rejected the April and July 1996 *Lunar News* teachings because of an expectation that the higher dose would generate an increased incidence of gastrointestinal side effects. None of Merck’s arguments withstands scrutiny. Merck’s fear defense was concocted solely for litigation: it is utterly inconsistent with the facts, with the science,

and with everything Merck said and did before this litigation inspired Merck to dream it up.

1. The Early Reports of Esophagitis Would Not Have Deterred A Person of Skill in the Art from Once-Weekly Dosing

Shortly after Merck launched 10 mg daily alendronate, anecdotal case reports began to appear in the literature describing isolated instances of severe esophagitis that the authors associated with the administration of the 5 mg and 10 mg Fosamax tablets.⁴ The evidence, however, showed that these events were exceedingly rare, occurring in about one of every 10,000 patients taking 10 mg of alendronate daily. (Markowitz 436-37). Indeed, it was their rarity and peculiarity that made them appropriate for medical case reports. The esophagitis cases were also for the most part reversible with proper treatment. (Markowitz 451). Although Merck attempted at trial to blur the distinction between these rare cases and the much more common mild, non-specific GI complaints, the two are not related. (Markowitz 448-49). The esophagitis case reports were associated primarily with tablets “sticking” in the esophagus because patients failed to follow the dosing instructions (i.e., so-called “pill esophagitis”), in contrast to non-

⁴ At trial, Merck referred to the use of the terms “serious” and “severe” within the arcane workings of the FDA. (Yates 542-43). Apparently, “severe” and “serious” are differentiated in part based on whether the patient was hospitalized, with “serious” effects defined counterintuitively as more severe than “severe.” The experts at trial did not observe such strict definitional niceties. For example, Merck’s expert, Dr. Fennerty, used the term “serious” to designate any effect that caused a patient to discontinue her medication. (Fennerty 304). “Severe” will be used here to designate esophageal effects of the type discussed in the case reports relied on by Merck, regardless of the FDA definition.

specific side effects, to which Merck did not assign a cause.⁵ (Markowitz 442; Fennerty 278-79).

By March 1996, just five months after its launch in the U.S., almost a half-million patients had been prescribed Merck's 10 mg daily alendronate product. (DTX6 at 8; Markowitz 436). By that time, approximately 50 severe esophagitis cases (most of the cases that were later discussed in the literature) had already been reported to Merck. Merck, however, did not view these reports as significant, and took no action. (Hirsch dep. 62-63). In fact, Merck did not respond to the esophagitis reports until it learned that a letter written by a well-known bone specialist discussing two of these cases was circulating within the Mayo Clinic Health System. (Hirsch dep. 54-56). The facts show a stark contrast between the hyperbolic description of this episode by Merck at trial (*see* Fennerty 254-59; Merck Opening Statement 76-77), and the delayed reaction of Merck at the time.

When Merck finally acted, Dr. Hirsch testified that it brought "all of its resources to bear" on the issue raised by these reports of esophagitis, and took "all appropriate actions." (Hirsch dep. 61-62). After investigating, Merck concluded that the pill esophagitis cases were caused primarily by the failure of patients to adhere to the dosing instructions. (DTX315; DTX6; Markowitz 442; Hirsch dep. 66, 82-84;).

In view of its conclusion about the cause of the problem, Merck dealt with it by reemphasizing the dosing instructions. (Yates 569; Fennerty 282; Russell 194-95; Markowitz 442-44). In March 1996, Merck disseminated a "Dear Doctor" letter, informing physicians about the "infrequent" cases of esophagitis, stating that in a "large

⁵ Pill esophagitis is inflammation of the esophageal lining caused by direct contact with a medication that sticks in the esophagus instead of transiting to the stomach. (Markowitz 438-39).

majority” of the cases patients appeared not to have complied with the dosing instructions, and advocating “strict compliance” with those instructions. (DTX34).

Merck’s Dr. Yates testified that, in addition, Merck’s sales representatives reemphasized the importance of the dosing instructions in meetings with doctors. (Yates 569). Merck took no other steps to deal with the issue. (Fennerty 282; Russell 195; Markowitz 444).

The evidence shows that after Merck acted, the reporting of these esophagitis cases fell to almost nothing – less than one report per 100,000 patient-treatment months. (Yates 568-69; Fennerty 283-84; DTX486). Although at trial Merck presented the esophagitis cases as if they stunned the medical community, in fact, the number of patients being prescribed alendronate doubled between March of 1996 and October of 1996 (*Compare* DTX197 at MK0249547 and DTX395 at MK0250139), and the sales of alendronate increased by 72 percent between 1996 and 1997. (DTX374 at MK0391652-53).

Merck later reported on the severe esophagitis cases in an October 1996 DeGroen *et al.* article in the New England Journal of Medicine. (DTX6). The DeGroen paper reports that 51 patients experienced adverse effects classified as “serious” or “severe” out of the 470,000 patients worldwide who had received prescriptions for alendronate to treat osteoporosis up to that time. (DTX6 at 1018). Teva’s gastroenterology expert, Dr. David Markowitz, testified that the extremely low incidence of these effects, and the description of the cases, led gastroenterologists to conclude at the time, as Merck had, that the likely cause of the problem was “pill esophagitis.” (Markowitz 435, 438; *see also* Russell 193; DTX6). Merck’s gastroenterology expert agreed. (Fennerty 282-83).

The evidence demonstrates that these esophagitis case reports would not have deterred a person of skill in the art from administering a higher weekly dose of alendronate for osteoporosis. (Russell 195; Markowitz 447-48, 451-52). In fact, the

cases would have motivated adoption of the invention. (Russell 195-97; Markowitz 447-48). First, the events were rare. In a March 1996 presentation to the FDA addressing the esophagitis cases, Merck stated that the number of severe cases reported to that time was actually *lower* than the number of esophagitis cases that would have been expected in the same general population regardless of whether they were taking the medication. (DTX197 at MK0249562). Indeed, there was no evidence that any expert at trial, including gastroenterologists who had examined thousands of patients for upper gastrointestinal complaints, had ever seen one of these cases. (See Markowitz 446). In fact, pill esophagitis is associated with many common medications, including antibiotics and antiinflammatory drugs like aspirin. (Markowitz 441). The actual incidence of such cases in the population of people taking alendronate hardly rose to the level of the expected background incidence. (DTX197 at MK0249562).

Second, there was no evidence that the severe esophageal side effects were dose-related. Merck's Dr. Hirsch testified that Merck could not determine a dose-response relationship between the administration of alendronate and the severe esophagitis cases because the cases were so rare:

Q. But you didn't have any evidence that there was a dose-related effect between alendronate and severe cases of esophagitis?

A. I think, I think the scientifically correct answer to that question is that there were too few cases to be able to determine if there was or was not a dose relationship and you just can't tell, if something doesn't happen with a certain frequency, you cannot tell if there is or is not a dose relationship.

(Hirsch dep. 52; *see also* Hirsch dep. 54 ("... the number of events of things like esophagitis was fairly small in the clinical trials and we could not determine with certainty whether there was or was not a dose-related effect.")). Thus, in July 1997 there

was no expectation that administering a higher dose once-weekly would be associated with a greater incidence or severity of esophagitis.

These severe esophagitis cases would not have deterred a person of skill in the art from administering higher once-weekly doses of alendronate to treat and prevent osteoporosis. In fact, the evidence presented at trial leads to the opposite conclusion. Once-weekly administration would have been expected to decrease the incidence of severe esophagitis cases because it would (1) improve patient compliance with the dosing instructions (Russell 195-96; Markowitz 485-86; Fennerty 311), which were intended to ensure safe passage of the drug to the stomach (Russell 127-28; Fennerty 310; Yates 627), and (2) decrease the frequency of administration, thereby decreasing the chances of a tablet “sticking” in the esophagus. (Russell 196-97; Markowitz 443).

2. The Evidence Does Not Support A Dose-Response Relationship Between Alendronate and Gastrointestinal Effects That Would Have Deterred A Person of Ordinary Skill in the Art From Once-Weekly Dosing

(a) The Chesnut Study Would Not Have Deterred Once-Weekly Dosing

Merck argues that the study by Chesnut establishes a dose-related gastrointestinal effect associated with the administration of alendronate to post-menopausal osteoporotic women, and that this effect would have discouraged a person of skill in the art from following the teaching in the *Lunar News* to use higher once-weekly dosing. The Chesnut results, however, even standing alone, do not represent a deterrent to following the teachings of the *Lunar News*. (Russell 184-85). That conclusion is reinforced when the Chesnut results are viewed in the context of all of the information available in July 1997. (Russell 185; Markowitz 451).

At trial, Merck's expert testified about excerpts from other papers that referred to the Chesnut data, and he tried to create the impression that each excerpt represented a different clinical study. (See Papapoulos 658-59). However, on cross-examination, Dr. Papapoulos was forced to admit that these other reports are derivative of Chesnut. (Papapoulos 702-05). The Chesnut study thus represents the only alendronate clinical data on which Merck's fear defense rests. (Yates 545).

In the Chesnut study, seven out of 63 post-menopausal osteoporotic women taking 40 mg alendronate per day dropped out of the study because of mild gastrointestinal adverse effects, compared with smaller percentages of dropouts in the groups taking lower dosages of alendronate daily. (Russell 183; DTX14). The side effects were not severe or serious like those in the case reports, but instead were mild and non-specific. (Russell 184-85).

Neither Chesnut nor his co-authors, including Dr. Santora, an inventor on the '329 patent drew any conclusion regarding the statistical significance of the reported results. Merck's witnesses at trial, however, testified that those results demonstrate a dose-response relationship between gastrointestinal side effects and the administration of alendronate that would have discouraged a person skilled in the art from giving larger once-weekly doses for osteoporosis. (Yates 539-41). The evidence does not support Merck's position.

First, the Chesnut data actually demonstrate that 90 percent of postmenopausal osteoporotic patients tolerated the 40 mg daily dose. (Russell 184-85). Moreover, the Chesnut study does not relate to weekly dosing; it reports on daily dosing. The daily dose used in Chesnut was 40 mg per day, or 280 mg per week, not 70 mg once per week. That a percentage of patients taking 280 mg of alendronate weekly discontinued their

medication because of mild gastrointestinal upset does not imply that a larger percentage would discontinue at 70 mg weekly. Finally, although Merck portrayed the 10 percent dropout rate reported by Chesnut as unacceptably high, it is the same as (or lower than) the dropout rate Merck's expert Dr. Papapoulos observed when he prescribed the 10 mg daily alendronate product in his clinical practice. He testified that approximately 10-12 percent of his patients taking daily alendronate for treatment of osteoporosis discontinued the product because of gastrointestinal complaints, but that he continued to prescribe the drug. (Papapoulos 651-52). Standing alone, Chesnut's reported discontinuation rate for 40 mg alendronate *daily* would not have deterred a person of skill in the art from giving either a 70 mg dose or a 35 mg dose *once-weekly* to treat or prevent osteoporosis. (Russell 184; Markowitz 450-51).

Indeed, before this litigation provided Merck with the motive to argue otherwise, its official position was that Chesnut's data supported the safety of Merck's proposed 70 mg weekly dose. In a formal 1998 presentation to the FDA seeking approval to conduct clinical trials on weekly dosing of 70 mg alendronate, Merck cited the Chesnut data as part of the evidence that weekly doses of 70 mg and 35 mg of alendronate for treatment and prevention of osteoporosis should be "very well tolerated." (DTX192 at 8). In that presentation, Merck cited the Chesnut data positively rather than negatively as it did at trial, advising the FDA that "90% of postmenopausal patients with osteoporosis remained on alendronate treatment at 40 mg daily for one year." (DTX192 at 8; *see* Russell 188-89). In fact, prior to this litigation, Merck never interpreted the Chesnut study as creating to an expectation that once-weekly dosing would not be adequately tolerated. (*See* DTX147 at MK0158265; DTX521 at 6; DTX2 at MK0223123). Merck's pre-litigation

view of the Chesnut report is correct; its litigation-induced contention is not credible and should be rejected.

(b) Dr. Fennerty's Testimony Regarding A Dose-Response Relationship Was Discredited

Merck's expert Dr. Fennerty testified, using overheated rhetoric, that the reports of the severe esophagitis cases (discussed above), the Chesnut study, and a 1997 study by Blank *et al.* in rats, "shocked" him at the time, and indicated to him that Merck might be seeing the "tip of an iceberg" of a toxicity problem. (Fennerty 269-70). This testimony is not supported by the facts.

First, Dr. Fennerty's opinions are directly contradicted by Merck's pre-litigation positions. In its presentations to the FDA, its letter to doctors, and its scientific publications, Merck never suggested or even hinted at the "potential epidemic of severe gastrointestinal injury" that Dr. Fennerty described. (Fennerty 254). To the contrary, Merck suggested that the severe problems actually occurred less frequently than might be expected. (DTX197 at MK0249562). In fact, Merck's only response to the rare instances of severe esophagitis cases was to emphasize its dosing instructions, and experience proved that Merck's response was entirely adequate to eliminate the problem in short order.

Second, Dr. Fennerty's testimony is not credible in light of the testimony of Dr. Markowitz, a gastroenterologist who in 1996-97 actually analyzed the gastrointestinal issues surrounding alendronate. (Markowitz 430-34; Russell 174-75). Dr. Markowitz testified that his contemporaneous investigations indicated that severe events were extremely rare with alendronate and that overall the drug was well-tolerated. (Markowitz 433). Dr. Markowitz's carefully considered conclusions, which were drawn at the time,

are consistent with Merck's conclusions before this litigation required Merck to adopt a different theory.

Third, Dr. Fennerty's testimony combines, with no scientific basis, reports of rarely-observed severe esophagitis, i.e., the case reports discussed above, with non-specific, mild gastrointestinal side effects that commonly occur in the general osteoporotic population, i.e., the effects reported by Chesnut. (See Markowitz 429; 448-49; DTX32 at 60). This combination of unrelated side effects and symptoms is misleading. Dr. Fennerty admitted that none of the patients discontinuing the Chesnut study did so because of severe esophagitis of the type discussed by DeGroen in 1996. (Fennerty 303-04). Further, in view of the high background incidence of these symptoms in the general population, there is no evidence of a causal relationship between the mild non-specific gastrointestinal symptoms and alendronate administration. (Markowitz 448-49; Sherwood dep. 196-97).

Fourth, Dr. Fennerty's testimony regarding the Blank paper, which reports on a study carried out with rats (PTX104), was discredited on cross-examination, with Dr. Fennerty eventually admitting that he did not know whether the results of the Blank study were applicable to humans, that he had never attempted to find out, and that if they were applicable to humans they predicted no difficulties with a 70 mg alendronate dose.

The Blank protocol is designed to induce lesions. To see any lesions at all, Blank was forced to administer alendronate at doses at least 750 times the daily dose administered to humans, and to administer them in conjunction with a drug known to cause gastric irritation. (Fennerty 288-89). On cross-examination, when asked to look more carefully at the data and to extrapolate them to human dosages, Dr. Fennerty admitted that the very plot he proffered as evidence of a "shocking" dose-response

relationship (Fennerty 269) predicted that *no discernible difference* between the gastrointestinal response to a 10 mg dose and the response to a 70 mg dose. In fact, Dr. Fennerty agreed that based on this plot the number of lesions expected using the 10 mg daily dose in human patients would be “virtually at zero,” and that the number of lesions expected at a 70 mg once-weekly dose would be “virtually next to it.” (Fennerty 292, 296; DTX526).

Realizing the implications of his admission, Dr. Fennerty retreated from his prior testimony and from the Blank study itself: he could not make the “assumption” that the injury pattern seen in humans and rats would be the same; he did not know the dose equivalency between rats and humans; the Blank study itself did not mean higher doses of alendronate were contraindicated; he had *never* investigated whether dosing in rats had any relationship to dosing in people; and, remarkably, he did not think that was necessary. (Fennerty 293-96).

In addition, Dr. Fennerty admitted that he was unaware that Merck’s own scientists had published a paper highly critical of the Blank study, which pointed out several flaws in its methodology. (Fennerty 298). Dr. Chennekatu Peter, the veterinary pathologist who designed and carried out the dog studies described in the ’329 patent (Peter dep. 53-54), published an article reporting on his own study of the gastrointestinal effects of bisphosphonates in rats. (PTX138). Dr. Peter reported that in his study, stomach lesions were only seen in rats to which alendronate was administered at doses “much higher” than (approximately 150 times) the doses used clinically in humans. (PTX138, Table 1). Dr. Peter then criticized the Blank study because the dose used by Blank were “very large in comparison to the recommended clinical dose for humans.”

(PTX138 at 1010). Thus, prior to this litigation, Merck's own scientists discarded the same data that its expert relied on in forming his opinions.

Dr. Fennerty's opinions were not based on a scientific examination of the evidence. For example, his superficial and careless approach to the Blank study, and the fact that he was forced to recant all his direct testimony about it, in particular illustrates that his opinions are not trustworthy. His testimony regarding the expected gastrointestinal response to a higher dose of alendronate was not credible and should be given no weight.

3. Before this Litigation, Merck Admitted that the Prior Art Data Available in July 1997 From Paget's Patients Showed that Once-Weekly Dosing Should Be Well-Tolerated

The data from the Paget's studies demonstrates that 40 mg and 80 mg of alendronate daily were well-tolerated, and that 40 mg daily was as well tolerated as placebo. In addition, by 1997, thousands of Paget's patients had taken the 40 mg daily dose clinically, with no greater degree of gastrointestinal complaints or severe complications. (Russell 190-91; Yates 608). Thus, the Paget's disease data provided compelling evidence that the once-weekly dose of 70 mg alendronate would have been well tolerated.

Confronted with the scientific evidence, most of it generated by studies supported by Merck and involving Merck scientists, Merck hatched a story for trial that the data generated in studies of Paget's patients cannot be used to draw conclusions regarding the tolerability of the drug in osteoporotic patients, and thus is irrelevant to the invention of claims 23 and 37 of the '329 patent. However, before this litigation provided Merck with a motive to adopt this story, its position, both internally and externally, was consistently the opposite.

Internally, in a May 20, 1997 “Tactical PAC” review seeking management approval to go forward with a once-weekly dosing program, Merck’s scientists relied on the Paget’s data to support the expected tolerability of the higher once-weekly dosing regimen. (DTX147 at MK0158265). Merck’s own analysis, presented to Merck’s management, confirmed that the Paget’s data supported the safety of the proposed regimen:

There is human safety data available on these higher doses. The largest experience is derived from the Paget’s Disease studies including data on over 150 patients randomized to receive 3-6 months of daily treatment with alendronate 40 or 80 mg. This data is supplemented by short term clinical pharmacology studies with doses up to 100 mg. In all theses [sic] studies, *the 40 and 80 mg doses were well tolerated even when given on a daily basis*, although daily treatment with alendronate 40 mg was associated with a moderate increase in upper GI adverse events in the Phase II study of treatment of osteoporosis (Protocol 026).

(*Id.*) (emphasis added). In view of the Paget’s data, Merck did not regard tolerability as a significant concern. To the contrary, Merck’s scientists stated that higher once-weekly dosing would be “*unlikely to have a greater potential to induce upper GI irritation.*” (DTX147 at MK0158265) (emphasis added). Indeed, the only concerns Merck had were economic: (1) whether a patent could be obtained for once-weekly dosing to “allow for extension of the FOSAMAX patent to 2018,” and (2) the potential negative impact of once-weekly dosing on “pricing.” (DTX147 at MK0158265).

Externally, in a March 1998 formal submission to the FDA, Merck maintained the position earlier taken internally that the data from Paget’s disease studies provides an expectation that a once-weekly dose would be well-tolerated:

Experience in Paget’s disease (up to 80 mg alendronate for 6 months) suggests that dosing regimens of either 35 or 70 mg weekly, and 35 mg twice-weekly should be well-tolerated.

(DTX192 at 17).

Elsewhere in that same document, Merck drew both on the Paget's data and the data from Chesnut in concluding that a once-weekly dose should be *very well-tolerated*:

Oral doses of alendronate up to 80 mg daily for up to six months have been well-tolerated in patients with Paget's disease, and approximately 90% of postmenopausal patients with osteoporosis remained on alendronate treatment at 40 mg daily for one year. *Thus, alendronate dosing regimens of either 35 or 70 mg once-weekly, and 35 mg twice weekly should be very well-tolerated.*

(DTX192 at 8 (emphasis added)). Slides for the FDA presentation held a few weeks later reiterated that "Evidence for Safety" was found in the Paget's studies where patients were treated with "80 mg/day for 3 to 6 months in 42 patients with good tolerability . . ."

(DTX521 at 6). In that same slide, it is noted that there had been "[f]ew reports of UGI [upper gastrointestinal] AEs [adverse events] from marketed use of 40 mg." (DTX521 at 6).

In 2000, all three inventors listed on the '329 patent co-authored a publication explaining the rationale for once-weekly dosing of alendronate. (DTX2). Under the heading "Safety and Tolerability Studies in Humans," the inventors once again cited the Paget's disease data as providing a "convincing" expectation that a once-weekly dosing regimen would be tolerated by osteoporotic patients:

Convincing human tolerability data for a higher dose of alendronate come from clinical trials of alendronate in the treatment of Paget's disease. Treatment with 40 mg alendronate daily for up to 1 year was associated with tolerability profiles comparable to those of the control agent (placebo or etidronate), and no patient discontinued alendronate treatment due to a serious drug-related adverse event.

(DTX2 at MK0223123). As support for that proposition, the inventors cited the Paget's disease studies by Siris, Reid, and Khan discussed *supra*.

Merck's pre-litigation documents, prepared for the most part by the inventors on the '329 patent, demonstrate that Merck's litigation story, that the Paget's experience is

irrelevant to the question of the expected tolerability of once-weekly therapy with alendronate, is not credible. Merck's story should be rejected.

4. A Person of Skill in the Art Would Not Have Been Deterred From Once-Weekly Dosing Because of the Alleged Dose-Related Effects of Prior Art Bisphosphonates

Merck also argued at trial that dose-related effects seen with prior art bisphosphonates would have created an expectation that alendronate would have dose dependent upper gastrointestinal side effects. This expectation, according to Merck, would have deterred a person of ordinary skill in the art from administering a higher once-weekly dose of alendronate for osteoporosis.

Merck argues that the data from pamidronate studies is especially pertinent because of the structural similarity between that molecule and alendronate. Specifically, Dr. Yates testified that "because of their structural similarity, actually one would expect them to be more similar than different."⁶ (Yates 617). This theory, like the other elements of Merck's fear defense, is not supported scientifically and is inconsistent with Merck's *ante litam motam* positions.

The sheer volume of data available in July 1997 from the use of the alendronate makes reference to other bisphosphonates unnecessary. By July 1997, orders of magnitude more data were available from clinical trials and clinical experience with alendronate in treating both osteoporosis and Paget's disease than for any other bisphosphonate. (Russell 162-64; Papapoulos 699-701; Fennerty 277-78). These data demonstrated that at every daily dose alendronate was well-tolerated. Merck offers no

⁶ The irony of Merck's current position should not be lost. In the prior litigation between these parties, Merck successfully argued that the properties of alendronate could not be predicted from those of pamidronate, and that the use of alendronate for osteoporosis was therefore not obvious.

support for its argument that a person skilled in the art would ignore all this information about the drug in question in favor of the limited data available for other drugs that were never approved for osteoporosis in the U.S.

In fact, in writing about bisphosphonates, Merck's expert Dr. Papapoulos warned against what Merck is trying to do here – use the experience from one drug to predict the effects of another. He wrote that because of differences in their mechanisms of action, as well as their pharmacological and toxicological profiles, results from one bisphosphonate cannot be extrapolated to the whole class:

Differences also exist in their pharmacological and toxicological profiles, as well as in their mechanism of action. It is, therefore important that the specific properties of every individual bisphosphonate be determined and that results obtained with one bisphosphonate not be extrapolated readily to the whole class.

(DTX527 at 543). When Merck itself considered the likely tolerability of its proposed 70 mg weekly dose, it did not consider data from the other bisphosphonates. Instead, it correctly recognized that those drugs were largely irrelevant in view of the vast pool of information about alendronate. Indeed, in the end, Dr. Papapoulos admitted that what he had written was correct, and that the data from the use of alendronate in Paget's disease was more relevant than the data from the prior art use of pamidronate. (Papapoulos 700-01). This conclusion was echoed by Teva's expert Dr. Markowitz:

- Q. And you would never make the correlation between the experience from pamidronate to alendronate?
- A. When I was reviewing the data, 500,000 patients or close to that number had already taken the drug alendronate, so there was much information on alendronate and positive GI events. So in drawing conclusions about how safe and well tolerated alendronate was, I can't imagine data on another drug, even if it was somewhat related, would inform my opinion about the drug alendronate.

(Markowitz 463-64). As with its attempt to discredit its own information from the Paget's experience, Merck's litigation-motivated effort to shift the focus to other bisphosphonates should be rejected.⁷

5. Merck's Own Physician Survey Demonstrated the Absence of any "Fear" of Higher, Less-Frequent Doses of Alendronate

Not only did the evidence at trial demonstrate that Merck's fear defense was not based on scientific evidence, the medical community responsible for patient care in fact did not harbor the fear that Merck argues would have deterred the administration of 70 mg once-weekly. In 1997, Merck undertook a marketing survey of physicians to ascertain how they would perceive several proposed new formulations and regimen changes. (DTX244 at MK0174863). This survey entailed "in-depth" interviews with 319 physicians in May and June 1997, just before Merck filed its patent application. (*Id.* at MK0174864). One of the alternatives about which Merck asked the physicians was less-frequent dosing, specifically twice-weekly. With regard to gastrointestinal upsets, these physicians perceived that larger less-frequent doses would result in "less GI upset:"

Twice weekly
 - Convenient/only twice a week
 - *Less frequent dosing = less GI upset*
 - Fits patients schedules

⁷ With respect to clodronate and etidronate, Dr. Russell testified that their side effects differed in both type and associated dose from those of alendronate. First, the clodronate and etidronate effects were primarily associated with the lower gastrointestinal tract (e.g., diarrhea), not the upper gastrointestinal tract (e.g., nausea and heartburn) that Merck has focused on in this case. Second, the effects were seen at doses 100 to 300 times larger than the doses used with alendronate. The doses of etidronate and clodronate generally associated with side effects were more than 1000 mg, and often more than 3000 mg. (Russell 162-63). Again, in light of the data available for alendronate in July 1997, results from the use of these other bisphosphonates are essentially irrelevant. (Russell 162-63).

(DTX244 at MK0174867) (emphasis added). The August 13, 1997 memorandum from Merck's marketing executive forwarding these results characterized them as demonstrating that "once-weekly" dosing appeared to be a "very strong" contender. (DTX244 at MK0174861).

This survey, which represent the only scientifically gathered evidence of physicians' perceptions of less frequent dosing of alendronate, demonstrates the bankruptcy of Merck's fear defense. Physicians had no "fear" of administering larger doses. The "perception" was, in fact, that larger less-frequent doses would cause "less GI upset."

The British court recognized Merck's fear defense for what it is: a theory ginned up solely for the purpose of litigation, which has no basis in the evidence. (See DTX405 ¶¶ 84-94). This Court, like the British court, should reject it.

D. The '329 Invention Does Not Provide "Unexpected Results"

Because the invention of claims 23 and 37 would have been obvious, and because the prior art disclosed its principal advantage – enhanced convenience and compliance – whether or not the invention provided other advantages not disclosed in the prior art is irrelevant. By virtue of the disclosures of *Lunar News*, the public had the invention; Merck cannot take it away from the public by alleging that it provided other benefits not described in the prior art. *In re Wiseman*, 596 F.2d 1019, 1023 (C.C.P.A. 1979).

Even if such undisclosed advantages were relevant, however, Merck would have the burden of establishing their existence, which it has failed to do. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *In re Inland Steel Co.*, 265 F.3d 1354, 1365 (Fed. Cir. 2001); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

The '329 patent states that the dosing regimen provides "less gastrointestinal effects," an advantage Merck touts as "unexpected." This alleged advantage, however, is not supported by scientific evidence. See e.g., *In re DeBlauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *Inland Steel*, 265 F.3d at 1365; *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). Since the gastrointestinal effects of 10 mg daily are comparable to placebo, the once-weekly regimen could logically demonstrate significantly "less" effects. Indeed, Dr. Russell testified without contradiction that no clinically significant difference exists between the two regimens in terms of gastrointestinal effects. (Russell 199-202). Dr. Santora, one of the inventors, testified that Merck could not claim a safety advantage for once-weekly dosing, and had never conducted a study that would support it. (Santora dep. 295-97).

The only data that Merck can allege that it had that was not possessed by people of skill in the art in July 1997 are the results of its dog studies. Merck's reliance on these studies is unfounded.

First, the asserted claims are limited to humans, so a result from an experiment on a beagle, whether expected or not, is not relevant. Second, the dog studies provide no data, expected or not, that is relevant to clinical experience. The designer of the studies, Merck's Dr. Peter, testified that the studies were never intended to provide information that was transferable to clinical treatment:

Q. I am trying to figure out whether you believe these dog studies have any bearing whatsoever on the clinical situation in which people take Alendronate sodium?

A. That was not the purpose of these studies.

(Peter dep. 81). Merck's gastroenterology expert echoed that sentiment, testifying that the studies have no relevance to the human clinical experience:

Q. And the study has no data that's relevant to the human experience; is that right?

A. Not directly relevant, no.

(Fennerty 314). The dog studies represent a science project. Whether or not they provide interesting information, they do not demonstrate that following the claimed method to treat or prevent osteoporosis provides any results that are "unexpected."

E. Merck Did Not Carry Its Burden On Commercial Success

At trial, Merck attempted to bolster the alleged nonobviousness of the invention of the '329 patent by touting the "commercial success" of its once-weekly alendronate products. Merck's attempt fails because Merck never connected any economic success with the claimed invention. Indeed, Merck made no attempt to do so, and its presentation ignored, rather than accounted for, the marketplace factors that influenced the sales of alendronate sodium.

Merck's burden was to demonstrate the commercial success of its invention, and to show that any commercial success was attributable to the invention. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("a nexus between commercial success and the claimed features is required"). In particular, because once-daily Fosamax is prior art and was itself a highly successful product, Merck was required to show that the once-weekly product contributed an incremental success beyond that of the once-daily product, and that this increment could be tied to the patented invention. Merck attempted to satisfy this burden by the use of a mathematical house of cards that collapsed at trial.

1. Commercial Success Cannot be Probative in this Case

Merck's effort to tie alleged commercial success to obviousness does not get off the ground because commercial success cannot be relevant under the circumstances of

this case. The rationale that justifies considering commercial success as evidence of obviousness is the theory that commercial success demonstrates that persons skilled in the art had an economic motivation to solve the problem that the inventor solved. That they did not do so, and that the inventor did, may show that the invention was not obvious to others with the motive to make it. *Chicago Rawhide Mfg. Co. v. Crane Packing Co.*, 523 F.2d 452, 459 (7th Cir. 1975), *cert. denied*, 423 U.S. 1091 (1976); *Cosden Oil & Chem. Co. v. American Hoechst Corp.*, 543 F. Supp. 522, 541 (D. Del. 1982); *Minnesota Mining & Mfg. Co. v. Research Medical, Inc.*, 679 F. Supp. 1037, 1054 (D. Utah 1988) (“Commercial success is considered relevant to lack of obviousness on the rationale that competitors would have been motivated to make the invention sooner if it had been truly obvious”).

This rationale, however, does not apply in this case. In relying on commercial success, Merck ignores that it was the only entity allowed by law to market alendronate for the first five years after it was approved. This new chemical exclusivity prevented any one else from marketing alendronate until September 2000 irrespective of any patent rights. See 21 U.S.C. § 355(c)(3)(D)(ii). Thus, no one else had the incentive to develop new dosing forms of alendronate because no one else could bring an improved dosage form to market. Accordingly, even if Merck could prove “commercial success,” that success would be irrelevant to the obviousness issue.

2. Merck Failed to Prove that the Once-Weekly Invention Contributed to Commercial Success

(a) Sales of Once-Weekly Alendronate do Not Prove Commercial Success

Merck’s expert, Dr. Vellturo, did not demonstrate any connection between the patented invention and Merck’s sales of once-weekly Fosamax. In fact, he did not even

opine that the two were connected, stating only that “commercial success could be at least in part, significant part, attributable to the Daifotis patents.” (Vellturo 715). This passing reference does not establish any connection between the alleged commercial success and the invention as described in the patent. In fact, the evidence indicates that any incremental success of the once-weekly Fosamax product was attributable to other factors.

After its introduction as a once-daily product in 1995, sales of Fosamax steadily increased. (DTX374). At the time the once-weekly product was introduced in 2000, the once-daily sales were still increasing. Merck claims that overall Fosamax sales increased dramatically when the once-weekly product was introduced. (Vellturo 718-19). However, the percentage increase in sales is much less dramatic than Merck claims.

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Thus, the sales figures, taken by themselves, do not show anything about the commercial success of the claimed invention. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1482-83 (Fed. Cir. 1997) (sales figures alone do not establish commercial success).

(b) Merck Failed to Consider other Market Factors

Merck’s emphasis on sales and prescriptions as the only indicia of success cannot establish that the once-weekly product was incrementally more successful than the prior art product – once-daily alendronate. Unlike Dr. Vellturo, Teva’s expert, Dr. Richard Rozek, an economist with many years’ experience actually analyzing the pharmaceutical

industry (Rozek 806-12), actually delved into the dynamics of the marketplace as it existed during the relevant period. As he pointed out, Merck failed to consider any of the other events that were occurring in the marketplace that contributed to the sales of once-weekly alendronate, and Merck did not consider several of its own initiatives and strategy choices that also affected those sales. (Rozek 814-15, 835).

Several significant events occurred in the osteoporosis treatment market immediately preceding or contemporaneously with the launch of Fosamax once-weekly. All these events tended to push sales up. Merck ignored these events, myopically attributing Fosamax once-weekly sales to the patented invention. (Rozek 814-15).

First, Merck failed to account for the effect of the increasing number of Americans over the age of 50. (Rozek 816-17). Merck used the number of women above the age of 50 as an estimate for people at risk for osteoporosis (DTX510 at 2), but this number is continuously increasing, a fact that must drive up the sales of osteoporosis treatments. (DTX355 at 2, 8 and DTX434).

Second, Merck ignored the fact that awareness of osteoporosis is always increasing. (Rozek 817-19). An increase in awareness of osteoporosis can come from many sources, including the National Osteoporosis Foundation, advertising by Merck and advertising by its competitors. Merck itself has vigorously attempted to raise awareness of osteoporosis through its promotional efforts, has tracked its effectiveness in doing so, and believes that even the actions of competitors are likely to increase awareness and drive sales. (DTX379 at MK0270410; DTX497).

The increase in the number of people seeking treatment for osteoporosis is another factor that Merck ignored. (Rozek 820-21). As of November 2000, the number of osteoporosis sufferers who are turning to drug therapy had nearly doubled from the

previous year. (DTX441). In addition, the number of people diagnosed with the disease has also increased. One indication of this is the increase in bone mineral density (BMD) testing. Merck's own documents discuss the increase in BMD testing sites, noting that in the number of BMD testing centers increased from 700 in 1995 to 12,000 in 2001. (DTX355 at 8). Merck acknowledges that increasing the number of women diagnosed with a BMD is "critical to the long term penetration of the osteoporosis market and the success of Fosamax." (DTX358 at MK0377332). Obviously, any increase in the number of people seeking osteoporosis treatment would have a positive effect on Fosamax sales.

Merck also overlooked the additional indications that Fosamax received from the FDA. Fosamax received several new approvals, including the indication to prevent and treat osteoporosis in men, at about the time of the once-weekly launch. (Rozek 822-25). These new indications had at least two benefits for Fosamax sales. First, new indications increase the number of potential users. (Rozek 824; DTX355 at 2). Second, a new indication gives the sales force a new reason to take its messages to doctors and reinforces existing positive clinical data. (Rozek 824; Counihan dep. 204-05).

Not only did many positive factors, all unconnected with the patented invention, converge at about the time Merck introduced once-weekly Fosamax, but other events had negative impacts on competitive products. (Rozek 825-26). These adverse events included an FDA warning Eli Lilly about its misleading advertising of Evista, reports on the lead content of calcium supplements and reports that hormone replacement therapy (HRT) increases the likelihood of breast cancer. (Rozek 825-30; DTX447; DTX450; DTX451). Merck itself recognized the opportunity that these events created for Fosamax.

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(c) Merck Ignores its own Successful Marketing Efforts

Merck attributes the sales of the once-weekly product to the merits of the invention. In fact, Merck's own extraordinary marketing efforts, undertaken at about the time of the launch of the once-weekly product, were designed to and no doubt succeeded in boosting sales.

First, Merck spent heavily on promotional expenditures in the quarter in which Fosamax once-weekly was launched.

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The reason pharmaceutical companies spend money on promotions is to increase awareness and sales of their products. (Rozek 839-40; Counihan dep. 41). In addition to the increase in promotional dollars that corresponded to the launch of the once-weekly product, Merck also changed the focus of its promotional expenditures to concentrate exclusively on the once-weekly product. (DTX355).

Sampling is another form of promotion, which is also effective to drive the use of a pharmaceutical product. (Rozek 841-42).

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Discounting the price of a pharmaceutical product has the effect of increasing sales. (Rozek 848). It is a fundamental law of economics that reducing the price of a

product will increase its sales. (Rozek 848).

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In short, the marketplace was highly complex, and a variety of important factors, unrelated to the '329 patent, contributed to changes in sales volume. Merck never even attempted to deal with these other factors.

3. Dr. Vellturo's Diffusion Model is Flawed

To camouflage its failure to consider the most basic marketplace factors, Merck's expert applied over it a veneer of economic sophistication in the form of a so-called "diffusion model." In essence, Dr. Vellturo gathered "cumulative new prescription" data for once-daily Fosamax, and fit it to an equation. He then extrapolated the once-daily sales as "predicted" by the equation, and assumed that this extrapolation is an accurate assessment of what would have happened in the absence of the once-weekly product. He noted that actual sales of Fosamax after the introduction of the once-weekly dose were higher than the "prediction," and assumed that any difference between the two is attributable to the advantages of Fosamax once-weekly. (Vellturo 737-38)

Dr. Vellturo's "model" was wrong in conception, wrong in application, and wrong in execution. A diffusion model is designed to measure the spread of an innovation through a specific social system that consists of potential "adopters" of the innovation. (DTX382). The authors of the paper on which Dr. Vellturo based his diffusion model state that diffusion modeling is not particularly useful as a forecasting tool, the use for which Dr. Vellturo employed it. (DTX382).

The use of a diffusion model to analyze Fosamax is also inappropriate because

several key assumptions underlying the use of a diffusion model do not apply to Fosamax. (Rozek 852). Diffusion models are relatively simple. In order for a diffusion model to be effective in modeling the spread of an innovation, certain restrictive, underlying assumptions must describe the innovation to be modeled, none of which apply to the Fosamax market. (DTX382 at 24-25):

- The number of potential adopters must not increase or decrease over time. (DTX382 at 24-25). As already discussed above, the number and percentage of Americans over the age of 50 is continually increasing. (DTX355 and DTX434). The authors of the paper on which Dr. Vellturo bases his diffusion model warn of this very situation, “if the fundamental diffusion model were applied to a diffusion process that is dynamic, incorrect parameter estimates and/or incorrect forecasts may result to the extent that [the number of potential users] fluctuates.” (DTX382). Dr. Vellturo claimed to have checked this assumption by using a diffusion model that allows for steady-state growth (Vellturo 733), but as Dr. Rozek pointed out, Dr. Vellturo did it wrong. (Rozek 859; DTX538).
- The product being analyzed must be independent of other innovations and products. (DTX382 at 24-25). This assumption does not describe Fosamax. (Rozek 853-54). Merck states that Fosamax competes with the other members of the FAME market and with other products such as hormone replacement therapy and calcium supplements. (DTX350; DTX362).
- The nature of the Fosamax product changed over time by the introduction of new indications. (Rozek 854-55). This characteristic violates another assumption for the appropriate use of a diffusion model. (DTX382, at 24-25).

- Fosamax exhibits “stages of adoption,” another factor not permitted by a diffusion model. (DTX382 at 24-25; Rozek 855-56). A diffusion model does account for users starting and then stopping use of the innovation, something that happens for Fosamax.

Finally, Dr. Vellturo’s model was fatally flawed because he used the wrong data to generate it. As a surrogate for “adopters,” Dr. Vellturo used “cumulative new prescriptions,” a parameter which, because it is cumulative, must in fact always increase over time. Yet the form of the equation Dr. Vellturo used requires that the number of adopters in the social system reach a maximum at some point. Thus, Dr. Vellturo’s model predicts an event, the leveling off of the number of adopters, that cannot possibly happen to the parameter he is modeling. (Vellturo 751-52). In other words, the model makes no sense from the beginning.

Indeed, that Dr. Vellturo’s methodology makes no sense is clear from the fact that it shows the same phenomenon no matter what date is used. That is, Dr. Vellturo claims to have demonstrated an upward break in actual sales compared to predicted sales that coincides with the introduction of once-weekly Fosamax. Yet he would have seen exactly the same phenomenon had he based his model on any other date. (Rozek 863-64). Thus, his model can predict whatever Merck wants it to demonstrate.

Merck never showed that the sales of once-weekly Fosamax were attributable in any way to the invention claimed in the ’329 patent, as distinguished from the benefits of the drug itself and the other factors that existed in the marketplace. For this reason, Merck has failed to satisfy its burden of demonstrating commercial success.

IV. THE '329 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT

A. Merck and Dr. Yates Intentionally Withheld the July 1996 *Lunar News*

Merck nowhere contests that the July 1996 issue of the *Lunar News* discloses the concept claimed in the '329 patent – the weekly dosing of alendronate for the management of osteoporosis. Notwithstanding that Merck and Dr. Yates had this reference, no one connected with Merck disclosed it to the examiner who allowed the '329 patent. The withholding of this reference was intentional, and the patent is therefore unenforceable for inequitable conduct.

Dr. Yates was charged with keeping abreast of the literature about bone disease in general and had a special responsibility to be aware of *Lunar* publications in light of his position with the Bone Measurement Institute (an entity created by Merck that had dealings with the principal makers of bone densitometers). (Yates dep. 20-23, 39-43). An employee in Merck's marketing department was responsible for tracking the comments made in the *Lunar News* in order to assess their impact on Merck and facilitate a response, if necessary. (Yates dep. at 18) From time to time, this employee distributed excerpts from the *Lunar News* that concerned Merck or its products to Merck scientists and executives. (DTX38; DTX50; Yates 533). Thus, Dr. Yates would occasionally receive copies or portions of the *Lunar News* for his review. (DTX38; Yates 533).

Among the portions Dr. Yates received were excerpts from the July 1996 *Lunar News* attached to a memorandum dated September 3, 1996. (DTX38; Yates 570-71). At that time, Dr. Yates's only responsibilities involved alendronate. (Yates 574). The memorandum states that one of the subjects addressed in the attached *Lunar News*

excerpts was “alendronate.” In fact, the attached excerpt contained the portion of the July 1996 issue that describes the once-weekly dosing of alendronate at 40 mg or 80 mg for osteoporosis. (DTX38 at 13). In the margin next to that description is a large handwritten question mark.

In 1997, the business relationship between Merck and Lunar Corp. deteriorated, and on February 7, 1997, Dr. Mazess wrote a letter to Ray Gilmartin, President of Merck, discussing that relationship. (DTX42 at MK0334167). Attached to the letter was the section of the July 1996 issue of *Lunar News* that discussed the once-weekly dosing of alendronate for osteoporosis. (DTX42 at MK0334177; Yates 576-77). Merck and Lunar Corp. agreed to meet to discuss their relationship and attempt to resolve the issues between the companies. (Yates 575). The agenda prepared by the parties contained as a line item Dr. Mazess’s letter to Mr. Gilmartin. (DTX44; Yates 576-78).

The meeting with Lunar Corp. took place on May 21, 1997, the day after Merck management had given Dr. Yates the go-ahead to develop the once-weekly dosage form of alendronate. (Yates 576-79). Among those attending for Merck were, in addition to Dr. Yates, two highly-placed executives for Merck, Dr. Louis Sherwood (Vice President of Medical and Scientific Affairs) and Dr. Jeremy Allen. Among those present for Lunar were Dr. Mazess, author of the *Lunar News*. (Yates 530-31; Beckman dep. 20-21; Mazess dep. 175-77).

At the May 21, 1997 meeting, Merck’s delegation was sharply critical of comments Dr. Mazess had made in the *Lunar News*. (Yates dep. 213). Dr. Sherwood, in particular, was upset about Dr. Mazess’s recommendations regarding the less frequent dosing of alendronate at a higher dose. (Weissburg dep. 18, 69). Indeed, Dr. Sherwood had previously complained about Dr. Mazess’s once-weekly dosing

recommendations when he approached Dr. Mazess at the American Society for Bone Mineral Research conference in Seattle in September 1996. (Mazess dep. 155-57).

Dr. Yates is an inventor on other patents, and in 1997 he had an understanding of the concept of "materiality." He acknowledged that the July 1996 *Lunar News* is material prior art to the '329 patent. Dr. Yates was also an active participant in the prosecution of the '329 patent. He attended the pivotal interview with the examiner that resulted in allowance of the claims. (DTX17 at 70). However, at no time during the prosecution of the application for the '329 patent did Merck or any of the inventors disclose that issue of *Lunar News* to the examiner. (Yates 575).

On August 26, 1998, Merck filed an "Information Disclosure Statement" in connection with the application for the '329 patent. With that statement, Merck included a disclosure from the April 1997 *Lunar News*, but did not disclose the July 1996 issue. (DTX17 at 63). The July 1996 issue of *Lunar News* is not cumulative of the April 1997 *Lunar News*. Whereas the April 1997 issue was published only a few months before the July 22, 1997 priority date for the '329 patent and potentially could have been eliminated as prior art by showing an earlier date of invention, the July 1996 issue was published almost a year before, and possibly more than a year before, the earliest filing date for the '329 patent. In addition, although the April 1997 issue discloses once-weekly dosing, the July 1996 issue discloses dosing at 80 mg per week, which is clinically indistinguishable from the claimed "about 70 mg." (Russell 137-38). It is therefore more material than the April 1997 issue in two different respects.

Dr. Yates's testimony (Yates 572-78) that he did not read either the *Lunar News* disclosures attached to the September 6, 1996 memorandum or the letter to Dr. Gilmartin, which was the subject of a meeting for which Dr. Yates traveled from New Jersey to

Wisconsin, is not credible. It is especially not credible in light of the testimony from other attendees of the May 21, 1997 meeting that the subject of once-weekly dosing and the *Lunar News* publication of that concept were discussed at that meeting. Dr. Yates must have been aware of the July 1996 *Lunar News* disclosure, and must have understood its materiality at the time. Under the circumstances, the Court should conclude that Dr. Yates acted with intent to deceive the patent examiner.

B. Dr. Yates's Conduct was Inequitable; the '329 Patent is not Enforceable

In the interests of effective patent examination and fairness to the public, applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty. 37 C.F.R. § 1.56. A violation of this duty renders all claims of the issued patent unenforceable. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1180-81 (Fed. Cir. 1995). To comply with this duty, applicants must disclose to the Patent Office all information they are aware of that is material to the examination of the application. *Critikon Inc. v. Becton Dickinson Vascular Access Inc.*, 120 F.3d 1253, 1256 (Fed. Cir. 1997).

To determine whether a patent is unenforceable, the trial court conducts a two-part analysis. First, it must determine if the statement or omission meets a threshold of materiality. Second, it determines whether the evidence shows a threshold level of intent to mislead the Patent and Trademark Office. *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1439 (Fed. Cir. 1991).

The July 1996 *Lunar News* was highly material. It specifically disclosed the invention (weekly dosing of alendronate), the motivation to make the invention (dosing inconvenience), and the dosage strength (80 mg, or "about 70 mg"). There can be no question that a reasonable examiner would have considered the reference important to the

allowability of the claims. *GFI Inc. v. Franklin Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001); *Halliburton*, 925 F.2d at 1440. Indeed, any argument that the reference is not material is foreclosed by Dr. Yates's admission that it is. (Yates 575).

The evidence shows that Dr. Yates acted with intent to deceive the examiner. This intent can be inferred from the surrounding circumstances. *Paragon Podiatry Lab., Inc. v. KLM Labs.*, 984 F.2d 1182, 1194 (Fed. Cir. 1993). Here, Dr. Yates's sole project was alendronate. In September 1996 he received a memorandum discussing *Lunar News's* comments about alendronate, and attaching the relevant portions of the July issue. His testimony that despite the fact that alendronate was all he worked on he did not read the attachments is not credible.

Likewise not credible is his testimony that he did not focus on the July 1996 issue again when he went to the May 21, 1997 meeting with Lunar Corp., at which the letter to Merck's president with its attached copy of the July 1996 *Lunar News* was an agenda item. His denial that once-weekly alendronate was discussed at the meeting is also not credible in light of the testimony of the other attendees.

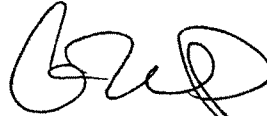
Because of the high level of materiality of the July 1996 *Lunar News*, the evidence establishes the requisite intent required to compel a holding of unenforceability. *Halliburton, supra*. The '329 patent is unenforceable because Dr. Yates intentionally failed to disclose the July 1996 *Lunar News*.

CONCLUSION

For the foregoing reasons, the Court should find that claims 23 and 37 of the '329 patent are invalid and unenforceable.

Respectfully submitted,

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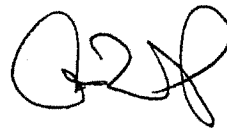
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EXHIBIT E

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

MERCK & CO., INC.,)	
)	
Plaintiff,)	
)	
v.)	Civil Action No. 01-048 (JJF)
)	(Consolidated)
TEVA PHARMACEUTICALS USA, INC.,)	
)	
Defendant.)	

**TEVA PHARMACEUTICALS USA, INC.'S
POST-TRIAL REPLY BRIEF**

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INTRODUCTION

Merck does not dispute that the July 1996 *Lunar News* discloses every detail of the invention of the asserted claims of the '329 patent to a person skilled in the art. Merck's argument that the publication does not anticipate those claims is based on its convoluted definition of "about," which Merck's own experts never endorsed, and on a misinterpretation of the patent law's "enablement" requirement.

Merck likewise does not dispute that to a person of ordinary skill in the art, the April and July 1996 issues of *Lunar News* teach both the claimed invention and the motivation for adopting it. Moreover, the evidence at trial showed that Merck's "fear defense" was baseless. The expectation of persons skilled in the art in July 1997 would have been and in fact was that once-weekly dosing would be safe and well-tolerated. Indeed, before Merck had the motive to concoct the fear defense, its consistent official position was precisely the opposite of the story it tried to present at trial. Before it needed the fear defense to shore up its patent, Merck told its management, the FDA and the public that prior experience with alendronate did not caution against the use of once-weekly administration, but instead affirmatively supported the safety of that regimen. Merck's sudden turnabout by itself demonstrates that the fear defense is groundless.

Similarly, in an attempt to avoid the impact of the prior art, at trial Merck floated Dr. Vellturo's "diffusion model" as the flagship of a commercial success argument. That model, however, sank without a trace, and Merck's post-trial submissions abandoned any attempt to salvage it. Merck's commercial success argument is not only not supported, it is irrelevant under the circumstances of this case.

The asserted claims of the '329 patent represent an attempt to claim as an invention what everyone skilled in the art knew and what others had explicitly disclosed. Claims 23 and 37 are both anticipated by and obvious in view of the prior art and are therefore invalid.

ARGUMENT

I. THE JULY 1996 *LUNAR NEWS* ANTICIPATES CLAIMS 23 AND 37

Merck does not dispute that the *Lunar News* discloses once-weekly administration of alendronate sodium for the treatment and prevention of osteoporosis. Nor does Merck dispute that the *Lunar News* discloses using “about 70 mg” and “about 35 mg” of alendronate sodium on an alendronic acid active basis for this purpose, as those terms would be understood by a person skilled in the art. Instead, Merck contends that the July 1996 *Lunar News* reference does not anticipate claims 23 and 37 of the '329 patent because the term “about” in claims 23 and 37 does not mean “about.” Instead, Merck proposes a construction that would make the word superfluous. Merck also claims that the reference is not “enabling.” Merck is wrong on both counts.

A. “About” Means “About”

Claim 23 requires administration of “about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis” and claim 37 requires administration of “about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.” Dr. Russell testified that to a person of ordinary skill in the art, 40 mg and 80 mg, both of which are disclosed in the July 1996 *Lunar News*, are “about 35 mg” and “about 70 mg,” respectively. (Russell 137-42). Dr. Russell’s testimony accurately reflects the ordinary

usage of “about,” i.e., “approximately,”¹ and Merck does not dispute that in the context of administering alendronate for the treatment and prevention of osteoporosis, to a person of ordinary skill in the art 80 mg and 40 mg are “about 70 mg” and “about 35 mg,” respectively. Instead, Merck claims that “about” does not in fact mean “about” because the specification has redefined it so that it has no meaning in the context of the claim. Merck attempts to support this contention by pointing to a sentence in the specification, which it claims defines the term “about.” Merck’s reliance on this sentence, however, is misplaced.

The threshold question in claim interpretation is the ordinary meaning of the terms of the claim. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). Merck does not dispute Teva’s and Dr. Russell’s application of the ordinary meaning of terms “about 70 mg” and “about 35 mg.” Instead, Merck argues that in this case the inventors have chosen to be their own lexicographers by providing an alternative definition. In doing so, Merck ignores that a claim term must be given its ordinary meaning unless the specification *clearly compels* a contrary interpretation. *Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001); *Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002) (emphasis added). The specification here does not meet that strict criterion.

Merck cites to only one sentence of the specification of the ’329 patent for its proposed alternative definition of “about”:

Because of the mixed nomenclature currently in use by those or [sic] ordinary skill in the art, reference to a specific weight or percentage of

¹ Webster’s Third New International Dictionary (1993); American Heritage Dictionary of the English Language (1978).

bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase “*about 70 mg of bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof and mixtures thereof, on an alendronic acid active weight basis*” means that the amount of bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.”

(Col. 10, line 65-col. 11, line 8 (emphasis added)). Merck argues that this text imparts a special meaning to the word “about.” According to Merck, the word is used to account for the fact that different alendronate salts have different molecular weights, and that to deliver the same amount of physiologically active compound to the bone they must be administered at slightly different dosage strengths.

Merck’s argument makes no sense, however, because the claim itself accounts for this phenomenon by directing that the compound be administered on the basis of a common denominator, i.e., “on an alendronic acid active basis.” That is, the claim requires that the amount of “alendronate sodium trihydrate” be sufficient to deliver the same amount of active material as “about 70 mg” of alendronic acid.² The word “about” therefore does not perform the function which Merck assigns to it, and must be in the claim for another purpose: to have its ordinary meaning of “approximately.”

As Dr. Russell testified, Merck’s interpretation of the patent text is a “curious use of the English language.” (Russell 338-39). In fact, if “about” is interpreted as Merck argues it should be, the term is meaningless as it appears in the claims:

Q: But in the patent it gives you a precise reference and says when we say about 70 milligrams of a bone resorption inhibiting bisphosphonate, what we mean is that amount of bisphosphonate

² In other words, because alendronate sodium has a higher molecular weight than alendronic acid, to deliver 70 mg on “on an alendronic acid active basis” Merck’s Fosamax tablets actually contain more than 90 mg of the salt. Similarly, to deliver 35 mg “on an alendronic acid active basis,” Merck’s Fosamax tablets actually contain more than 50 mg of the salt. (DTX394).

that will deliver an equivalent amount, the equivalent of 70 milligrams of alendronic acid; correct?

A: Yes. I have difficulty with this statement because the reason if it's that precise at 70, why does it use the phrase about?

(Russell 338-39). As Dr. Russell concluded, although the sentence to which Merck points is intrinsically confusing, its purpose is not to define the term "about," but only to illustrate what is meant by "on an alendronic acid active basis:"

Q: When you read that, and when you read it now, is it your understanding as somebody skilled in the art that that's a definition of the word "about"?

A: It's definitely not an English dictionary definition of the word "about."

Q: They're defining what is meant by acid active weight basis, but they're not defining what is meant by "about"; is that right?

A: Yes.

(Russell 403-04). Merck's experts offered no testimony about their interpretation of the passage on which Merck relies, and Dr. Russell's testimony on this issue is unchallenged. Thus, the specification of the patent does not *clearly compel* an alternative meaning of the term "about," and the ordinary meaning must control.

The ordinary meaning must control for another reason as well. The Federal Circuit has repeatedly held that every limitation in the patent claim must have some meaning. *Exxon Chemical Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557 (Fed. Cir. 1995), *cert. denied*, 518 U.S. 1020 (1996), *quoting In re Sabatino*, 480 F.2d 911, 913 (C.C.P.A. 1973) ("Claim limitations defining the subject matter of the invention are *never* disregarded"); *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991) ("All the limitations of a claim must be considered meaningful"). Yet as discussed

above, Merck's redefinition of the term "about" would effectively read the term out of the claim, because the function Merck assigns to it is fulfilled by the reference to "alendronic acid active basis." Merck's interpretation is therefore wrong. Since Merck does not dispute that the ordinary meaning of "about 70 mg" and "about 35 mg" encompass the 80 mg and 40 mg dosage strengths disclosed in the July 1996 *Lunar News*, that publication anticipates claims 23 and 37.

B. The July 1996 Lunar News Disclosure is Enabling

Merck also argues that July 1996 *Lunar News* disclosure does not anticipate claims 23 and 37 of the '329 patent because it is not enabling. Again Merck is wrong. This time Merck misconstrues the enablement requirement. Merck concludes that the *Lunar News* reference could only be enabling if it addressed the alleged expectation of physicians in the field that alendronate sodium administered at higher doses would not be safe and well tolerated. Merck's conclusion is based on its assertion that "when the invention is a method of treatment, it is not enabled when the expectation is that the treatment's side effects would not be tolerable and safe." Not surprisingly Merck cites no legal authority for this proposition, because none exists.

A prior art reference is "enabled" if it allows a person of ordinary skill in the art to carry out the invention. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003); *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). The July 1996 *Lunar News* meets this definition. The invention, as described in claims 23 and 37 of the '329 patent, is the treatment or prevention of osteoporosis by oral administration to humans of "about 70 mg" or "about 35 mg" alendronate on a once-weekly basis. The July 1996 *Lunar News* teaches exactly that. Furthermore, 40 mg alendronate tablets were

commercially available, so that a patient could easily take one or two of them to arrive at the 40 mg and 80 mg strengths that *Lunar News* describes. In any case, even in the absence of commercially available tablets, it would have been “trivial” to make a dosage form containing the suggested amount. (Santora dep. 159, 162).

Finally, Merck’s expert Dr. Papapoulos admitted that the *Lunar News* reference would have enabled a person of ordinary skill in the art to practice the invention before July of 1997. He conceded that if such a person had administered oral alendronate according to the *Lunar News* disclosure, it would have been a safe and effective therapy for dealing with osteoporosis. (Papapoulos 670-71).

The fact that patients were not actually administered alendronate according to the method disclosed in the *Lunar News* does not negate that the *Lunar News* is enabling. “It is not . . . necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.” *In re Donohue*, 766 F.2d at 533; *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.*, 246 F.3d 1368, 1379 (“Rather, anticipation only requires that those suggestions be enabling to one of skill in the art”); *In re Samour*, 571 F.2d 559, 563n.6 (C.C.P.A. 1978) (“[W]hether or not [the claimed invention] had been made previously is not essential to a determination that a method of preparing it would have been know by . . . one of ordinary skill in the art.”).

Moreover, it is irrelevant whether a physician would have expected the method of treatment disclosed in the *Lunar News* to be safe and tolerable. In *Bristol-Myers Squibb Co.*, several of the claims at issue were directed to a method of treating cancer by, *inter alia*, premedicating the patients. The Court found a prior art reference to be enabling and to anticipate these claims, even though the reference did not describe premedication, and

even though the reference stated “further studies are needed to see if pretreatment regimens . . . will permit the *safe administration* of this compound.” *Bristol-Myers Squibb Co.*, 246 F.3d at 1378-79 (emphasis added). Thus, even if the prior art reference explicitly states that safety testing needs to be done, it is nevertheless enabling.

Finally, Merck’s importation of a “safety and tolerability” requirement into the enablement analysis is a poorly disguised attempt to assert the fear defense where the law prohibits it. By asserting that the July 1996 *Lunar News* is not enabling because it fails to address expectations about safety and tolerability, Merck is in effect asserting that the prior art “taught away” from the invention. Although the evidence demonstrated that the fear defense is bogus and that the prior art did not teach away from the invention, it is also well established that “teaching away” has no bearing on the issue of anticipation. *Bristol-Myers Squibb Co.*, 246 F.3d at 1378 (“[T]he question of whether a reference ‘teaches away’ from the invention is inapplicable to an anticipation analysis.”). Since claims 23 and 37 do not contain a safety or tolerability limitation, the safety and tolerability issues are not relevant for purposes of anticipation.

The dosing regimen covered by claims 23 and 37 of the ’329 patent was available to the public almost a year prior to Merck’s alleged invention date. Merck’s patent claims must therefore be held invalid under 35 U.S.C. § 102(a).

II. TEVA PROVED BY CLEAR AND CONVINCING EVIDENCE THAT THE CLAIMED INVENTION WOULD HAVE BEEN OBVIOUS IN JULY 1997

Merck clings to the argument, built on irrelevant scraps of information and half truths, that persons of skill in the art would have tossed aside the teachings of the *Lunar News* because of a “fear” or “expectation” that the obvious once-weekly dosages would

lead to unacceptable side effects. (Merck's Opening Br. at 30-31). However, Merck cannot escape that before this litigation provided Merck with a motive to argue otherwise, Merck scientists relying on the same prior art Teva relies on here stated unequivocally that once-weekly dosing was "*unlikely* to have a greater potential to induce upper GI irritation" than daily dosing. (DTX147 at MK0158265 (emphasis added)). This statement, made before Merck filed for the '329 patent, similar subsequent statements made by Merck and its scientists, and the reported perceptions of physicians prescribing alendronate, demonstrate that the alleged "fear" of increased side effects with once-weekly dosing never existed, and was made up for this case.

Far from showing an "expectation" of failure with once-weekly dosing, the evidence unequivocally demonstrates the opposite: in July 1997 once-weekly dosing was expected to be well-tolerated. Each piece of the rickety contraption that is Merck's fear defense collapses under scrutiny, and with it Merck's rebuttal to Teva's proof that claims 23 and 37 are invalid.

A. The Facts Proving Obviousness are Not in Dispute

Merck nowhere argues that the April and July 1996 *Lunar News* articles do not teach the invention of claims 23 and 37 of the '329 patent. In fact, these references unambiguously disclose once-weekly administration of alendronate for osteoporosis. Merck does not dispute that motivation existed to administer alendronate once-weekly. Likewise, Merck concedes that in July 1997 a person skilled in the art would have understood the appropriate weekly doses to be 70 mg and 35 mg for treatment and prevention of osteoporosis, respectively. (Papapoulos 682, 684; Russell 149-50; 152-53). Moreover, Merck admits that in July 1997 "those of skill in the art knew that once-

weekly administration of alendronate would be efficacious.” (Merck Opening Br. at 29). For these reasons, a person of skill in the art reading the April and July 1996 *Lunar News* would have recognized that the references describe an effective method of treating and preventing osteoporosis. Thus, no dispute exists regarding the salient facts: in July 1997 the prior art expressly taught once-weekly dosing for osteoporosis, it provided the motivation to do so, it taught the appropriate doses, and it taught that the regimen would be effective. In view of those facts, the invention of claims 23 and 37 would have been obvious and those claims are therefore invalid under 35 U.S.C. § 103(a). (See Teva Opening Br. at 24-28).

B. Teva Proved a Reasonable Expectation of Success in July 1997

Merck argues that in July 1997 an “expectation” existed “that alendronate sodium doses higher than 20 mg presented an unfavorable tolerability and safety profile,” and that because the *Lunar News* did not address this expectation, the claimed invention cannot have been obvious. (Merck Opening Br. at 30-31). This argument fails (1) factually, because the evidence shows that no such expectation of an unfavorable tolerability and safety profile existed (Teva Opening Br. at 27-44), and (2) legally, because Merck misstates the requirement for an expectation of success under section 103.

Merck’s argument amounts to a contention that to be effective as prior art the *Lunar News* had to set forth *proof* that the disclosed method would have a “favorable” tolerability profile (which Merck nowhere defines). (See Merck Opening Br. at 30). Since the ’329 patent itself includes no such proof of or claims to any such profile, Merck’s argument implies that the prior art must show more than the ’329 patent itself shows or claims. That is not the law. “Obviousness does not require absolute

predictability of success.” *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). In *O’Farrell*, the patent applicant argued that a prior art article that disclosed “virtually all” the claimed method nevertheless failed to render the claimed invention obvious because of unpredictability in the field. According to the applicant, the article offered nothing more than “speculation” that had never been carried out, and that it was therefore not certain at the time the reference was published whether its disclosure could be carried out. According to the applicant, without such certainty, the prior art disclosures, which “hindsight” demonstrated were correct, were “merely invitations” to make the claimed invention. *Id.* at 902. The Federal Circuit rejected that standard, holding that for obviousness “all that is required is a reasonable expectation of success.” *Id.* at 904.

Like the applicant in *O’Farrell*, Merck argues that Teva’s case is “rooted in hindsight.” (Merck Opening Br. at 30). According to Merck, because it did not provide certainty of success, the *Lunar News* teachings of once-weekly dosing were “nothing more than an unsupported shot in the dark.” *Id.* This argument is indistinguishable from the contention squarely rejected in *O’Farrell*. The law does not require “certainty”; instead, it requires a “reasonable expectation of success.” *Id.* at 904; *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985); *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Merck does not dispute that Teva has proved by clear and convincing evidence that in July 1997 a “reasonable expectation” existed that once-weekly alendronate would have an acceptable tolerability profile. Moreover, Teva demonstrated that Merck repeatedly relied on the same evidence prior to this litigation to convey that same expectation of tolerability.

1. Merck's Emphasis on a "Dose Related" Effect is Misplaced Because the Prior Art Taught that Alendronate should be Safe at the Relevant Doses

Merck spends much of its brief arguing that persons skilled in the art in July 1997 would have known that "bisphosphonates" demonstrated "dose-related" gastrointestinal effects. This argument is a red herring. Even if Merck had proved that those skilled in the art would have speculated that ever-higher once-weekly doses might lead to "increased" side effects at some point, that speculation would be irrelevant here because those same persons *knew* the results of administering the doses of alendronate required for once-weekly treatment and prevention of osteoporosis, i.e., "about 70 mg" or "about 35 mg" respectively.³ In July 1997 persons of skill in the art knew from the prior art that *daily* doses of 40 mg and 80 mg were well-tolerated. (Teva Opening Br. at 16-18). Whether a "dose-related" side effect might show up at a still higher dose is irrelevant.

Merck itself relied on those same results. Internally before management, and externally before the FDA and the scientific community, Merck repeatedly characterized the prior art to the '329 patent as demonstrating that once-weekly doses of alendronate for osteoporosis would be well-tolerated. (Teva Opening Br. at 38-41). Merck's scientists told management in May 1997, just two months before the '329 patent application was filed, that "40 and 80 mg doses were well tolerated *even when given on a daily basis.*" (DTX147 at MK0158265 (emphasis added)). The bottom line is that, like Merck's own scientists, persons of skill in the art in July 1997 knew what happened at the relevant doses of "about 70 mg" and "about 35 mg." At those doses, alendronate was

³ In every instance, Merck neglects to state whether doses were being administered daily or weekly. Merck argues about side effects seen with "10 mg," "20 mg," and "40 mg" doses, but it never makes clear that those doses were administered daily, and thus do not reflect side effects that would be seen with single once-weekly doses.

well-tolerated. Whether at even higher doses, a “dose relationship” would lead to unacceptable side effects is irrelevant to the question of what would have been expected at the claimed doses. (*See* Teva Opening Br. at 38-41).

2. Merck Confuses Different Types of Side Effects To Cloud the Issues In this Case

Merck misleadingly lumps together the severe esophagitis cases seen early in the marketing of alendronate with mild non-specific symptoms that have never been proved to be associated with alendronate. For example, Merck states that the severe esophagitis cases were “a warning flag” about the “viability of alendronate” in the treatment of “elderly postmenopausal women,” and that “[s]ince the gastrointestinal side effects associated with bisphosphonates had long been reported to be dose related, increasing the dose was contrary to prevailing medical thinking.” (Merck Opening Br. at 2). These statements contradict what Merck knew and recognized before this litigation provided a motive to confuse the record: the rare, severe esophagitis cases and the more common general “gastrointestinal side effects” were unrelated.

Neither Merck nor anyone else ever viewed the esophagitis cases as calling into question the “viability of alendronate.” The evidence is in fact directly contrary. Merck never mentioned, suggested, or even hinted to the FDA or to the public that the severe esophagitis cases might affect the viability of the drug. These “pill esophagitis” cases were very rare; in fact, their number did not rise to the expected incidence of such cases in the treated population. (DTX197 at MK0249562). Merck did not react to the “warning flag” until it was forced to do so for public relations reasons. (*See* Hirsch dep. 54-56, 62-63). Moreover, Merck responded simply by reemphasizing the dosing instructions for alendronate in a letter to physicians and in meetings between its sales

personnel and doctors. After that response, which Merck's executives and Teva's witnesses agree was complete and appropriate, the rare events became even more rare. (Hirsch dep. 61-62; Yates 568-69; Fennerty 283-84; Markowitz 459-60; DTX486).

Moreover, prescribing physicians did not doubt the "viability of alendronate." Their practices belie the "anxiety" Merck ascribes to them; physicians *doubled* the number of alendronate prescriptions they wrote from approximately 500,000 in March 1996 (when the "clarion call" went out regarding the esophagitis cases) to one million when Merck met with the FDA just seven months later. (DTX197 at MK0249547; DTX395 at MK0250139). Doctors recognized what Dr. Markowitz understood at the time: the rare esophagitis case were anomalies, attributable largely to patients' failure to comply with dosing instructions, and unrelated to the dosage strength. (Markowitz 433-41). These cases did not represent a deterrent to prescribing the drug for other patients. (Teva Opening Br. at 30-32).

Not only did the severe esophagitis cases not deter doctors from continuing to prescribe and indeed expanding the number of prescriptions of once-daily alendronate, they would not have been a deterrent to once-weekly dosing in July 1997. To the contrary, the evidence shows that once-weekly dosing would have been expected to *decrease* the number of severe "pill esophagitis" cases by decreasing the number of tablets administered and increasing patient compliance with the dosing instructions. (Russell 195-97; Markowitz 441-43, 447, 485-86; Fennerty 310-11; Yates 627).

Merck cites the testimony of Dr. Fennerty for the proposition that the "gastroenterology community" thought that the severe esophagitis cases indicated that "we may be sitting on the tip of an iceberg of [a] potential epidemic of severe

gastrointestinal injury.” (Merck FF 52). As discussed in Teva’s Opening Brief, Dr. Fennerty’s overwrought testimony is not credible. Dr. Fennerty’s testimony is contrary to Merck’s own statements to the FDA and the medical community regarding the severe esophagitis cases. Dr. Fennerty’s testimony is also contrary to that of Teva’s Dr. Markowitz, a gastroenterologist who, unlike Dr. Fennerty, actually investigated the esophagitis case reports in 1996-97 in conjunction with well-known bone researchers. Indeed, Dr. Fennerty’s testimony demonstrated that he did not bother to investigate whether the articles that formed the basis for his alleged “alarm” in 1996, in particular an article about rats by Blank *et al.*, bore any relationship to the effects seen with alendronate in the clinical setting.⁴ (Teva Opening Br. at 35-38).

Finally, Dr. Fennerty mixed together the severe esophagitis cases with evidence of general non-specific gastrointestinal complaints, something that Merck’s scientists made clear was improper because the latter effects could not be attributed to alendronate with certainty. In particular, Dr. Anastasia Daifotis, one of inventors on the ’329 patent, stated that although the severe esophagitis cases could be causally associated with alendronate, the general complaints could not because of the background incidence of such complaints in the general population:

Based upon a complete review of data from large, randomised studies and postmarketing experience with alendronate, the only GI adverse experiences that have been causally associated with alendronate are rare esophageal events, generally presenting as retrosternal pain or burning or difficulty swallowing. These events must be discerned from general complaints of abdominal discomfort, which commonly occur in this population, irrespective of treatment with alendronate.

⁴ As discussed in Teva’s Opening Brief, Dr. Fennerty admitted at trial that when the data from the Blank study is properly analyzed, it predicts that there would be “no discernible difference” between the gastrointestinal side effects expected with 10 mg and 70 mg doses. (Teva Opening Br. at 36-37).

(DTX32 at 60). Merck's reliance on Dr. Fennerty's testimony, and its misleading pooling of information regarding severe esophagitis cases and general non-specific gastrointestinal complaints, are deliberately misleading and scientifically baseless.

Likewise unavailing is Merck's reliance on a "study" by Ettinger, which was published in 1998. First, the report was not published until after the filing date of the '329 patent, and could not have informed the person of skill in the art. Second, Merck's reliance on Dr. Papapoulos's testimony that Ettinger's "findings" were "clinically extremely important" is misplaced. (Merck FF 53). On cross-examination, Dr. Papapoulos admitted that the report was "not scientifically very interesting." (Papapoulos 694). In fact, Dr. Papapoulos understates the difficulties with the Ettinger report; it is junk science, and Merck's inventor, Dr. Yates, said as much on several occasions. For example, in an October 9, 1998 press release, Merck strongly criticized the Ettinger article as "scientifically inaccurate" and "potentially harmful to patients":

We strongly disagree with the conclusions of both articles and believe them to be not only scientifically inaccurate, but also potentially harmful to patients.

(DTX534 at MK0165968). With regard to the discontinuation rate Ettinger reported for patients taking alendronate, which Dr. Papapoulos said "confirms what every single clinician was seeing in daily practice," Merck said that the reported percentage of patients experiencing gastrointestinal symptoms was "entirely consistent with the known prevalence of such disorders in the general population." (*Id.*). In a letter to the editor of the journal that published Dr. Ettinger's report, Dr. Yates echoed the conclusions of Merck's press release, characterizing Dr. Ettinger's conclusions as "not supported."

(DTX273 at MK0232110). Merck's reliance on the Ettinger study here, after having so resoundingly disparaged it in the past, illustrates the weakness of Merck's case.

3. The Chesnut Data would Not have Deterred Once-Weekly Dosing

Merck's final refuge is the Chesnut study, but that report provides no shelter. According to Merck, the Chesnut study demonstrates that alendronate exhibits a dose-related effect that is peculiar to postmenopausal osteoporotic women (and apparently no other patient population) that would have deterred a person of skill in the art from administering alendronate at the claimed once-weekly doses. Merck states that the Chesnut data led Merck's scientists to avoid doses larger than 20 mg daily in postmenopausal osteoporotic women. (Merck Opening Br. at 12-13). However, in order to gain approval for a once-weekly clinical trial, Merck told the FDA exactly the opposite of what it told the Court. In a formal submission to the FDA, Merck and Dr. Yates stated that the Chesnut data (along with data from Paget's studies) supported the conclusion that once-weekly alendronate should be "very well tolerated." In stark contrast to the ominous spin Merck places on Chesnut now when it is attempting to salvage its patent, before the FDA Merck presented the Chesnut data positively, stating that the study demonstrated that "90% of postmenopausal patients with osteoporosis remained on alendronate treatment at 40 mg daily for one year." (DTX192 at 8). No witness at trial contradicted that conclusion, and it confirms the testimony of Teva's experts that the results of the Chesnut study standing alone would not have deterred a person of skill in the art from administering alendronate for osteoporosis on a once-weekly basis. (Russell 184-85; Markowitz 450-51).

Moreover, viewed in context, together with all the data available on daily doses of alendronate, the Chesnut data would not have deterred once-weekly dosing. When the Chesnut data are viewed in the context of the data available in July 1997 from the administration of 40 mg alendronate *daily* to postmenopausal women (Harris study), up to 80 mg daily to Paget's patients in clinical trials (Siris, Reid and Khan studies), and 40 mg daily to thousands of Paget's patients in clinical practice, the person skilled in the art would have believed that the once-weekly administration of 70 mg alendronate would have at least a "reasonable probability" of success. (Teva Opening Br. at 16-18, 32-35).

4. The Prior Bisphosphonates are Irrelevant

Merck points to the data from the use of the old bisphosphonates etidronate, clodronate and pamidronate as part of the evidence for its argument that persons skilled in the art understood that there was a "dose-relationship" between the administration of bisphosphonates and gastrointestinal side effects. (Merck's Opening Br. at 7-10). Merck's retreat to this argument is remarkable, in view of its position in the litigation involving the '077 patent that alendronate was such a leap forward in bisphosphonate therapy as to be incomparable to any prior compound.

In July 1997, vastly more information was available on the use of alendronate (the compound in question) than about the older bisphosphonates, which had by then largely fallen into disuse. (Papapoulos 699-701; Russell 162-64; Fennerty 277-78). Thus, data from the older compounds are irrelevant and reference to them unnecessary. (Russell 161-65; Markowitz 452-53; 463-64).

In addition, the side effects associated with etidronate and clodronate were largely unrelated to the upper gastrointestinal side effects that were of concern for alendronate,

and were attributable in part to the much larger doses employed for those compounds (e.g., 100-300 times higher than the doses of alendronate). (Russell 163-65; *see also* Merck FF 23, 31). At these enormous doses, the principal side effect seen with the use of etidronate and clodronate was diarrhea, which is not an upper gastrointestinal phenomenon. The record is devoid of any report linking diarrhea and alendronate at any dose. Thus, the etidronate and clodronate side effect experience is irrelevant to the expectation that persons of skill in the art would have had about the once-weekly administration of 70 mg and 35 mg of alendronate in July 1997. Merck citations to Dr. Russell's observations about dividing the etidronate and clodronate doses to deal with diarrhea are beside the point, as is its reliance on what Dr. Russell did or did not mention to Dr. Fleisch about those compounds.

Merck also relies on experience with pamidronate, and again notes that alendronate has "only one more carbon atom" than pamidronate (Merck FF 42), a fact that Merck previously told this Court was irrelevant to whether the compounds could be expected to have similar properties. Merck asserts that Ciba-Geigy discontinued research on pamidronate after esophagitis was observed in one of the clinical trials,⁵ and that in light of all the evidence on pamidronate, including Dr. Papapoulos's personal observations, a person of skill in the art would conclude that pamidronate demonstrates dose-related gastrointestinal effects. (Merck Opening Br. 8-10; Merck FF 34). However, like etidronate and clodronate, the evidence from pamidronate is not relevant to the claimed invention.

⁵ Merck implies that Ciba-Geigy withdrew its pamidronate product from development because of the esophagitis it observed. However, no witness with personal knowledge of Ciba-Geigy's decision-making ever testified to that fact.

Before this litigation, neither Merck nor Dr. Papapoulos had ever extrapolated from pamidronate side effects to those of alendronate. On the contrary, in 1995, Merck's scientists contrasted the relative absence of gastrointestinal side effects observed with alendronate from the experience with prior bisphosphonates, including pamidronate and etidronate:

Dose-dependent upper gastrointestinal irritation is the primary side effect associated with several other bisphosphonates, which are administered at higher doses.

(DTX276 at 1441; *see* Russell 161-62). Dr. Papapoulos also distinguished sharply between alendronate and the other bisphosphonates, admitting that information from the use of alendronate in Paget's disease patients, which demonstrated that 80 mg daily was well-tolerated, was more relevant than information from the administration of pamidronate. (Papapoulos 700-01). This testimony is consistent with his pre-litigation writings, which state that because of significant differences between bisphosphonates, results from one bisphosphonate should not be extrapolated to others. (DTX527 at 543). Describing and comparing the gastrointestinal side effects of alendronate and pamidronate in 1999, Dr. Papapoulos did not mention dose-relatedness with regard to alendronate side effects, but drew a sharp distinction with pamidronate, stating that "[w]ith oral pamidronate, GI effects appear to be dose-related." (DTX527 at 547).

Finally, Merck's attempt to extrapolate from pamidronate to alendronate fails on its own terms. Dr. Papapoulos testified that pamidronate administered at 150 mg per day for osteoporosis was a "very good" product, that it was as well-tolerated as daily alendronate, and that he used daily pamidronate for osteoporosis even after its development was halted. (Papapoulos 645-46).

The drug at issue here is alendronate. At the relevant time, the information available about that drug demonstrated, as Merck repeatedly stated, that weekly dosing at 70 mg and 35 mg would be safe and effective. Merck's arguments based on discredited attempts to extrapolate from non-analogous observations about remotely related compounds are scientifically unsound and should be rejected.

5. Merck's Arguments about Weekly Risedronate and Intravenous Alendronate are without Merit

Merck argues that Dr. Russell's not advising Proctor & Gamble to make a once-weekly version of its own bisphosphonate, risedronate, after reading the *Lunar News* in 1996, is evidence that Dr. Russell did not believe that the claimed invention was obvious before this litigation. (Merck Opening Br. at 21). This argument is silly. The claimed invention of the '329 patent relates to alendronate, not risedronate, and the April and July 1996 *Lunar News* articles do not mention risedronate, much less its weekly dosing. Thus, evidence of Dr. Russell's opinions concerning risedronate in July 1997 is irrelevant to the obviousness of the claimed invention.

Likewise baseless is Merck's contention that Dr. Russell's suggestion to use intravenous alendronate to avoid gastrointestinal effects implies that he did not believe that once-weekly alendronate was obvious. (Merck Opening Br. at 21). Intravenous alendronate had been used and described in the literature prior to July 1997, and it had been shown to be effective. (DTX400; DTX192 at MR0066685). Thus, in mentioning intravenous alendronate administration, Dr. Russell was simply summarizing what was disclosed in the literature. The passage pointed out by Merck is not Dr. Russell's exhaustive assessment of all of the possible means of administering alendronate. It is one

idea. Moreover, the fact that several means exist to address an issue does not make any one of them non-obvious. *See In re Heldt*, 433 F.2d 808, 812 (C.C.P.A. 1970).

6. Physicians Did Not Harbor a “Fear” of Higher Less-Frequent Doses

In the end, all Merck’s various attempts to build the image of perceived intolerability of alendronate at larger, less-frequent doses collapse in light of Merck’s own study of what prescribing physicians said they expected before the patent application was filed in July 1997. (Teva Opening Br. at 43-44). Far from expressing “fear” of increased doses administered less frequently, the consensus of hundreds of physicians in 1997 was that “less frequent dosing = less GI upset.” (DTX244 at MK0174867). This evidence that doctors were not “afraid” of giving larger, less-frequent doses contradicts Merck’s unsupported arguments about physicians’ perceptions.

In the same vein, Merck argues as “proof” that the *Lunar News* was not “enabling” the fact that “no one suggested it or carried forward the torch of once weekly dosing.” (Merck’s Opening Br. at 6). This statement is not true. In fact, in June 1996, shortly after the publication of the April 1996 *Lunar News* and more than a year before Merck filed the ’329 patent application, Merck’s executives in Europe became aware of a group of Italian clinical investigators seeking permission to pursue a clinical trial on once-weekly alendronate. (See Drake dep. 70-72). These executives notified Merck personnel in the U.S., and by August 1996 all three of the inventors listed on the ’329 patent had in turn been notified. (Daifotis dep. 92-93; Santora dep. 179-81; Yates dep. 106-08; *see also* Wold-Olsen dep. 86-88). Thus, Merck knew even before it filed its the patent application that the “torch of once weekly dosing” would have been carried forward by others had Merck allowed them to do so.

7. Merck's Scientists Believed Increased Gastrointestinal Effects Were "Unlikely" Based on the Evidence Provided in the Prior Art

In May 1997, Merck's scientists (including Dr. Yates) told Merck management that once-weekly administration of alendronate was "unlikely to have greater potential to induce upper GI irritation." That conclusion was based on the data from Paget's patients and the data from the Chesnut study. (DTX147 at MK0158265; Yates 581-82, 584-87). Merck's scientists had no expectation of increased gastrointestinal side effects at once-weekly doses.

Although Merck will likely argue that the conclusions of its scientists were bolstered by the results of its dog experiments, that argument does not withstand scrutiny. In May 1997, the only pertinent dog experimental results Merck had were the initial comparisons of the effects of five consecutive exposures to acidic alendronate solution to a single exposure with the same solution. (Yates 592). Although the designer of the dog experiments testified that they were not intended to predict anything about human patients (Peter dep. 65-67), Dr. Yates testified that the initial data spurred the conception of his invention. (See Merck FF 92-93). Irrespective of Dr. Yates's mental processes, the prior art report by Sorrentino (PTX98) had already disclosed what Dr. Yates said he concluded from the initial dog experiments, and had disclosed that conclusion with respect to patients taking alendronate tablets, not dogs whose innards were bathed with alendronate solutions. Faced with this prior art disclosure, Dr. Yates retracted his testimony and instead testified that the invention was supported by later experiments comparing daily administration with one solution to single exposures with a more concentrated solution. (Yates 558). Those later "high dose" experiments, however,

were not available in May 1997 when Dr. Yates stated that once-weekly dosing was “unlikely” to demonstrate increased gastrointestinal effects.⁶ (Yates 592). Thus, when Merck’s scientists concluded that once-weekly administration of alendronate was likely to be well-tolerated, they possessed the same information relied on by Teva here.

C. Merck’s Arguments that the Paget’s Data Should be Disregarded Are Groundless

Teva’s proof that a person of skill in the art would have reasonably expected once-weekly dosing of alendronate to be adequately tolerated was based in part on the results of studies in Paget’s patients. Merck argues that these results are irrelevant because, according to Merck, in 1997 it was generally accepted that one “could not extrapolate from Pagetic patients to osteoporotic patients.” (Merck Opening Br. at 18). In the end, Merck’s argument is impeached by its own repeated reliance on the Paget’s data to support the expected tolerability of once-weekly dosing. (Teva Opening Br. 38-41). Merck’s attempts to shore up its position do not rely on scientific evidence, but instead are based on irrelevant sideshows.

1. Merck’s Argument That the Paget’s Data Should Be Disregarded is Without Scientific Basis

Merck offered no scientific basis for its position that a person skilled in the art would have ignored the data from the Paget’s disease clinical trials in assessing the tolerability of alendronate in osteoporosis patients. The best that Merck could do was to

⁶ In fact, the Lufkin article about pamidronate, which Merck relies upon heavily, illustrates the same phenomenon with pamidronate as that disclosed by the initial dog experiments. Lufkin demonstrated in people that daily administration of 150 mg pamidronate resulted in esophagitis, while *weekly* administration of pamidronate did not. (PTX87 at 321 (five patients taking 150 mg pamidronate daily developed esophagitis while none of the patients taking the drug weekly developed that condition)). That is the same result observed with the initial dog experiments: repeated daily exposure irritated the dog esophagi, while a single exposure did not.

offer Dr. Papapoulos's opinion that physicians treating both Paget's patients and osteoporosis patients would "probably" understand that the two conditions would have different "toleration level."⁷ (Papapoulos 710-11). This conclusory opinion, that "physicians" would have such an "understanding" is without support in the scientific literature. Merck could not produce one article, book, or other reference demonstrating scientifically that the gastrointestinal tracts of Paget's patients and osteoporosis patients are somehow different, or that Paget's patients are more "stoic." In fact, the evidence at trial showed that Paget's patients and osteoporosis patients are more alike than different.

Both osteoporosis patients and Paget's patients exhibit a spectrum of clinical signs, extending from basically nothing to extreme pain and deformity.⁸ (Teva Opening Br. at 7). In 1997 both Paget's patients and osteoporosis patients who were not experiencing any pain or symptoms were treated with alendronate. Indeed, Merck's expert, Dr. Papapoulos, was forced to call into doubt the inerrancy of Dr. Fleisch's "bible" when he disagreed with the statement in the 1996 edition that treatment should be offered to all symptomatic and asymptomatic Paget's patients. (Papapoulos 691-93). No basis exists for the "pain-related" stoicism that Merck says differentiates Paget's patients

⁷ Although this testimony, offered on redirect examination after the opportunity to cross-examine had passed, is devoid of scientific underpinnings, and is at odds with Merck's own use of the Paget's data, it was also beyond the scope of the cross-examination. Teva objected at the time, and the Court should therefore disregard it. *United States v. Riggi*, 951 F.2d 1368, 1375 (3d Cir. 1991).

⁸ Merck calls osteoporosis an "asymptomatic disease." (Merck FF 69). That is not true. As support for this unqualified characterization of osteoporosis generally, Merck cites to Dr. Russell's testimony that "some" patients may be "asymptomatic in terms of bone pain." Setting Merck's distortion of the record aside, the evidence in this case overwhelmingly shows that osteoporosis is a serious disease that results in decreased quality of life, pain, deformity, especially of the spine, and, if accompanied by fracture, increased mortality. (Russell 111-12, 115-16). Merck's attempt to downplay the seriousness of the disease is curious in light of its concomitant argument about the huge commercial success Merck has experienced with alendronate.

from osteoporosis patients, and thus no basis exists for Merck's unqualified assertion that Paget's patients are "highly motivated to accept treatment." (Merck FF 71).

In fact, the conduct of clinical trials ensures that the Paget's disease clinical trial data with respect to side effects are directly applicable here. In most clinical trials, the investigators specifically question the patients about side effects – they do not merely record complaints. Thus, even those patients who are less likely to complain about non-serious side effects in clinical practice would still report them in a clinical trial. (Markowitz 425-26; Russell 176-79).

In addition, the use of a placebo control can ensure that the alleged "stoicism" of Paget's disease patients does not bias the results. The Reid study (of which Dr. Yates is a co-author) demonstrated that the Paget's disease patients who received 40 mg alendronate every day had no greater incidence of side effects than those patients receiving placebo. This use of a control corrects for any bias inherent in the patient population. (Russell 409-10).

At the end of the day, Merck and its scientists cannot escape their prior admissions. As Teva demonstrated at trial, before it needed to hatch a theory to support its patent, Merck repeatedly cited the Paget's disease data as supporting the notion that once-weekly alendronate would be well-tolerated in osteoporosis patients. (Teva Opening Br. at 38-41). The admissions of Merck and its scientists confirm that in July 1997 the scientific evidence demonstrated a reasonable expectation that once-weekly administration of "about 70 mg" and "about 35 mg" alendronate for treatment and prevention of osteoporosis would be well-tolerated. (Markowitz 449-52). Merck's fear defense does not withstand scrutiny, and claims 23 and 37 of the '329 patent should be

found invalid because the claimed invention would have been obvious in view of the prior art.

2. Merck's Attacks on Dr. Russell Are Unfounded

Unable to find scientific support for its fear defense, Merck is reduced to attacking Dr. Russell, accusing him of changing his position, and of making statements inconsistent with his prior expressed beliefs. Merck's accusations are false.

(a) Dr. Russell's Not Editing Every Line of Dr. Fleisch's Book Proves Nothing

At trial Merck produced a copy of proofs of Dr. Fleisch's book that included some handwritten editorial suggestions Dr. Russell had supplied in 1999 as a friendly favor to Dr. Fleisch. Apparently Dr. Fleisch, desperate to preserve his income stream based on Merck's sales of Fosamax,⁹ turned over to Merck's lawyers his private correspondence with Dr. Russell, which included these notes. Dr. Fleisch's book contains a statement in the section on alendronate that makes two observations without citation to any authority: (1) that alendronate was well tolerated up to a daily dose of 20 mg, but that at 40 mg daily *some* post-menopausal osteoporotic patients had "signs of upper gastrointestinal intolerance," and (2) that 40 mg daily was well tolerated in patients with Paget's disease. (*See* Merck Opening Br. at 18). According to Merck, Dr. Fleisch's observations prove that osteoporosis patients and Paget's patients tolerate alendronate differently. Merck further asserts that Dr. Russell's not suggesting changes to the way in which those observations are expressed demonstrates his agreement with Merck's interpretation.

⁹ Merck admits that Dr. Fleisch receives income from sales of Fosamax. (Merck opening 80). The amount of that income is such that Merck and Dr. Fleisch insisted that the details of the arrangement be admitted into evidence in the prior litigation under seal.

In fact, the quotation from Dr. Fleisch's book that Dr. Russell did not change is nothing more than two factual observations: Chesnut observed that some osteoporosis patients treated with 40 mg daily experienced gastrointestinal intolerance, and 40 mg daily is well-tolerated in Paget's patients. Those facts do not support Merck's conclusion that it was "generally accepted" in 1997 that one could not "extrapolate from Pagetic patients to osteoporosis patients." (Merck Opening Br. at 18). In 1997, Merck's scientists were extrapolating from Paget's disease patients to osteoporosis patients (and relying on the Chesnut data) to support their contention that once-weekly dosing was "unlikely" to exhibit increased gastrointestinal side effects in osteoporotic patients. (DTX 147 at MK0158265). Indeed, Merck's scientists continued to repeatedly extrapolate from Paget's disease to osteoporosis until this litigation. (Teva Opening Br. at 38-41).

That Merck would attempt to use as scientific "evidence" its distortion of Dr. Fleisch's book and the absence of editorial comments from Dr. Russell that would have prevented that distortion demonstrates how little substance Merck's case has. This incident vividly illustrates the adage that "no good deed goes unpunished." Dr. Fleisch, whose income is related to Merck's winning this case, showed up at trial for the sole purpose of bringing along the private comments provided by his old friend Dr. Russell and turning them over to Merck's lawyers. The fact that in 1999 Dr. Russell did not foresee the nonsensical inference Merck was going to draw from Dr. Fleisch's observations and edit them to head off that inference is not proof that Dr. Russell agreed with the spin Merck places on those few sentences now. Merck's argument that Dr. Russell is changing his story is silly.

Although what Dr. Russell did or did not suggest with respect to Dr. Fleisch's prose style is irrelevant, that Merck did not call Dr. Fleisch to testify is itself noteworthy. He traveled from Switzerland and was in the courtroom throughout the trial. He is certainly motivated to help Merck because, if Merck loses this case and generic competition enters the market, Dr. Fleisch stands to lose a source of income. Notwithstanding Merck's characterization of him as the "father" of bisphosphonates and the author of what Merck calls the bisphosphonate "bible," Merck did not call him to testify and have him describe the state of clinical knowledge. In fact, notwithstanding his contributions to physiological research on bisphosphonates, Dr. Fleisch could not shed light on these questions because he does not do clinical research, and does not see or treat patients. (Papapoulos 705; Russell 95). The statements Merck relies on from Dr. Fleisch's book are derivative of other researchers' work. Dr. Fleisch has no personal knowledge about the clinical aspects of the bisphosphonates his book discusses.

(b) Dr. Russell's Canadian Declaration has Nothing to Do With Gastrointestinal Side Effects

Merck also relies on a declaration that Dr. Russell submitted in a Canadian litigation relating to a patent on a complicated regimen for cyclical administration of etidronate. According to Merck, this declaration also indicates that Dr. Russell is changing his story and "adopting" Teva's position. This too is wrong.

Dr. Russell's declaration was limited to opinions concerning the obviousness of a cyclical protocol for treating and preventing osteoporosis with etidronate. (PTX297 at ¶58). This protocol is specific to etidronate, and the declaration had nothing to do with alendronate. Dr. Russell offered his opinion that it would not have been obvious that intermittently administered low doses of etidronate would be effective to treat

osteoporosis. In particular, Dr. Russell was responding to another declaration that stated that the *dosing regimen* for etidronate in osteoporosis could be gleaned from studies in Paget's patients. It is in this context that Dr. Russell states "[t]here is no precedent from the studies on etidronate in osteoporosis from which one could predict effective *doses*." (PTX297 ¶ 76 (emphasis added)). Dr. Russell explained at trial that his declaration dealt with selection of dosing regimens for different diseases, not whether to expect undue gastrointestinal side effects:

Q. Now in this case, you are extrapolating from Paget's disease to osteoporosis; correct?

A. In this case here?

Q. Yes.

A. Yes. But in relation to the gastrointestinal side effects, not in terms of how you would determine doses, which is the topic under discussion in the paragraph that you're showing on the board there.

(Russell 375). That testimony was not challenged.

Dr. Russell also testified that the "side effects" alluded to in Merck's snippets from his Canadian declaration refer to impairment of bone mineralization. That is, although editronate inhibits bone resorption, it also inhibits the formation of the mineral component of new bone, a side effect not associated with alendronate. Thus, the "side effect" to which Dr. Russell referred was not an upper gastrointestinal side effect, and has nothing to do with the issues in this case. (Russell 375-76).

Dr. Russell's Canadian declaration says nothing about extrapolation of gastrointestinal side effects from Paget's disease patients to osteoporosis patients. Merck's deliberate misrepresentation of this evidence by itself demonstrates how little support Merck can find for its positions.

Merck's attempt to impeach Dr. Russell were based on trivialities and misrepresentations. Dr. Russell's expertise was unchallenged, and the substance of his opinions were soundly based on the scientific evidence, and in the end were consistent with every representation Merck itself made before the need to salvage the '329 patent provided it the motive to advance its current theories.

D. Merck Did Not Prove "Unexpected Results"

Merck's attempt to imply that once-weekly alendronate provided an "unexpected result" is unsupported.¹⁰ Merck relies on a paper by Schnitzer *et al.*, which Merck characterizes as "acknowledg[ing] that once-weekly dosing of alendronate sodium could be a better dosing regimen." (Merck FF 95). This statement, according to Merck, confirms the results of Merck's dog experiments. However, Merck's assertion that once-weekly dosing "could be" better shows that Merck has no evidence that it is. The evidence does not support the conclusion that once-weekly dosing is superior to daily dosing in terms of gastrointestinal side effects.

Schnitzer could not say that once-weekly dosing was significantly better than daily dosing with regards to gastrointestinal side effects because daily dosing had been demonstrated to be indistinguishable from placebo. In fact, the Schnitzer study could not demonstrate significant differences between once-weekly and once-daily dosing because it was not adequately powered to do so, i.e., it was not large enough. Merck's Senior Director of Clinical Research, Dr. John Orloff, testified that the Schnitzer study could not prove the superiority of once-weekly dosing because daily dosing demonstrated an incidence of gastrointestinal side effects similar to placebo:

¹⁰ It is also irrelevant. *See* Teva Opening Br. at 44.

Q. But as you testified earlier, the Protocol 118 was not designed to distinguish any differences in safety profiles between the once-weekly dosing and the daily dosing, is that correct?

A. We did not have sufficient power based on our prior experience in clinical studies to be able to show a lower incidence of upper GI events, given that in studies of similar size, the daily dosing regimen had an incidence that was similar to placebo. So in these clinical studies of this size, we did not have power to be able to discern that.

(Orloff dep. at 13, 50-51; *see also* Santora dep. 199-200).

With regard to the statement from Schnitzer cited by Merck that there was “a trend toward a lower incidence” of gastrointestinal side effects with once-weekly dosing, Dr. Orloff testified that “it wasn’t statistically significant.” (Orloff dep. 59-60). One of Merck’s other inventors, Dr. Daifotis, agreed that there was no statistically significant difference between patients on 10 mg daily and patients on 70 mg once-weekly with respect to any single type of gastrointestinal event. (Daifotis dep. 338-39). Thus, any attempt by Merck to imply that once-weekly dosing provides a significant advantage over once-daily dosing must be viewed skeptically. Indeed, Dr. Russell testified that there is no evidence of a clinically significant safety advantage in administering alendronate once-weekly instead of once-daily. (Russell 198-200). That testimony was unchallenged.

E. Merck Failed to Demonstrate “Commercial Success”

Merck’s post-trial submissions include several claims about the purported commercial success of once-weekly Fosamax. First, Merck asserts that the commercial success of a product that embodies a patented invention is a factor that should be considered in determining whether an invention would have been obvious. This proposition is uncontroversial in an appropriate case, i.e., a case in which, unlike this one, others were free to compete with the patentee. Merck, however, does not address this threshold issue: whether, in view of Merck’s FDA-granted exclusivity for alendronate that precluded competition for the first five years of Fosamax marketing, commercial success is even a relevant inquiry. (*See* Teva Opening Br. at 46-47 and cases cited therein). Second, even if commercial success is relevant here, the evidence taken as a whole is not sufficient to demonstrate that any commercial success seen with once-weekly Fosamax is attributable to the invention claimed in the ’329 patent.

1. Merck Failed to Demonstrate a Nexus between the Success of Fosamax and the Invention of the ’329 Patent

Merck ignores its obligation to demonstrate the connection between any success of the product and the claimed features of the invention. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) (“A nexus between commercial success and the claimed features is required.”); *Riverwood International Corp. v. Mead Corp.*, 212 F.3d 1365, 1367 (Fed. Cir.), *cert. denied*, 531 U.S. 1012 (2000) (a trial court did not err in finding that (1) the patent owner “presented some evidence of commercial success” but (2) “much of that success was attributable to factors outside the scope of claims 1 and 13 of the . . . patent.”). Although the Fosamax 35 and 70 mg once-weekly tablets embody the claimed invention, those products embody

much more. The efficacy and safety of alendronate were known well before the introduction of Fosamax once-weekly, and those attributes made once-daily Fosamax a hugely successful product. (Russell 144-45; Papapoulos 667-71; Yates 548-49). Indeed, “a market leader who led with sales of a prior product cannot establish a nexus by the fact that it led with a new product.” *Nursury Supplies, Inc. v. Lerio Corp.*, 45 U.S.P.Q.2d 1332, 1333 (M.D. Pa. 1997).

Merck has not carried its burden here – to establish that the incremental success, if any, of once-weekly Fosamax was attributable to the claimed features of the invention. *See Pfaff v. Wells Electronics, Inc.*, 124 F.3d 1429 (Fed. Cir.1997), *aff’d*, 525 U.S. 55 (1998) (court discounted evidence of commercial success in view of patentee’s failure to establish that the success was attributable to the barb element, the only element not disclosed in the prior art). In fact, Merck’s documents state that the efficacy of the product is the primary consideration motivating doctors and patients to use Fosamax (DTX381 at MK0369615 and DTX499 at MK0334115), and for osteoporosis therapy, the efficacy of once-weekly dosing is identical to that of once-daily dosing. (Russell 144-45; Papapoulos 667-71; Yates 548-49). At best, Merck has proved the undisputed fact that once-weekly Fosamax is a successful product.. Merck has not proved, however, that any commercial success was attributable to the features of the claimed invention that were not disclosed in the prior art.

2. Merck Abandoned its Attempt to Demonstrate a Nexus

The sales of once-daily Fosamax were increasing from the day Merck introduced it, and were still increasing on the day Merck launched Fosamax once-weekly. Thus, to try to show commercial success of the once-weekly product, Merck attempted to

demonstrate that the sales growth for Fosamax was greater than it would have been in the absence of the once-weekly dose. To this end, Merck's expert Dr. Vellturo created a mathematical "diffusion model." The evidence at trial, including the cross-examination of Dr. Vellturo, showed, however, that the diffusion model was so riddled with flaws and inappropriate assumptions that Merck has apparently abandoned it altogether. (*See* Teva Opening Br. at 52-54). Despite the fact that the diffusion model was the centerpiece of Merck's commercial success case, it received not a single mention in Merck's post-trial brief.

In addition to not connecting the patent to the success of the product, Merck also failed to consider and account for other factors in the marketplace that would have had a positive impact on Fosamax once-weekly sales. These factors coalesced about the time of the launch of once-weekly Fosamax, and all of them favored Fosamax over its competitors. (Teva Opening Br. at 48-51). In addition, Merck has ignored that its own actions drove the sales of Fosamax. (*Id.* at 51-52). These efforts included increased promotional expenditures and a shift in marketing focus exclusively to the once-weekly product. (DTX355 at 4 and DTX344).

Attempting to downplay the effects of its own promotional efforts, Merck asserts that the alleged increase in sales occurred without a corresponding increase in promotional expenditures. (Merck Opening Br. at 32-33). However, during the quarter in which Fosamax once weekly was launched, such expenditures were the third highest ever for Fosamax. (DTX344). Merck presumably does not spend its promotional money unless it expects those expenditures to generate additional sales. To argue that the

Merck's sudden increase in promotional spending at the same time it was launching once-weekly Fosamax had no effect on sales of that product is not credible.

3. Teva's ANDA Filing Does Not Demonstrate Commercial Success

Perhaps recognizing the failure of its attempt to prove commercial success, Merck now relies on Teva's filing of an Abbreviated New Drug Application ("ANDA") as "the most undeniable indicium of commercial success." (Merck Opening Br. at 32). Teva's ANDA filing is irrelevant to the issue here: whether the success of Fosamax is attributable to the claimed invention. That Teva chose to seek approval to market a generic version of the weekly product shows that Teva believes once-weekly Fosamax is a successful product, a fact not in dispute. The filing is not, however, evidence that the success is attributable to the invention claimed in the '329 patent, as distinguished from other factors.

The fact that Teva is seeking to compete with a once-weekly product only tends to show that that product is supplanting the once-daily version. As Merck's expert Dr. Vellturo recognized, however, mere "switching" from the daily form to the weekly regimen does not establish the incremental commercial success necessary (but not sufficient) to demonstrate a connection between the patented invention and commercial success. In fact, Merck's documents show that Merck's marketing efforts were directed to switching the marketplace to a "Once Weekly World," and to the elimination of the daily dosing form. (*See* DTX355 at 24 and 33). Merck has focused all its promotional efforts on the once weekly product (Counihan dep. 153-54), and has discontinued sampling of the daily product. (Counihan dep. 145-47). Obviously, to the extent Merck has switched the market over to once-weekly, Teva has been required to follow that

market. Merck again misses the point: merely because the product is successful does not mean that it is a “commercial success” under the patent law. Such commercial success must be attributable to the invention of the patent, not to other factors, including, for example in this case, Merck’s actions to influence the market.

4. Merck’s Sales of Once-Weekly Fosamax Do Not Establish Commercial Success

Having observed the demise of its pseudo-scientific diffusion model theory of commercial success, Merck now emphasizes the sales figures and the dollar sales growth for Fosamax. A more appropriate measure of success, however, is the percent increase from year to year. The average increase in sales from 1996 through 2000 was 42.2 percent. (DTX374 and PTX166). The percentage increase for 2001, the first full year of once-weekly sales, was virtually the same – 42.5 percent. (DTX374). By Merck’s own estimate the percentage increase in 2003 will be only 28 percent (DTX362 at 46), the second lowest yearly increase in the history of the Fosamax franchise. Thus, sales of once-weekly Fosamax have merely continued the trend established by the once-daily product, which has the identical therapeutic benefits.

Attempting to make its sales figures appear dramatic, Merck misrepresents the significance of a chart prepared by Dr. Rozek. (Merck Opening Br. at 33; PTX299). Dr. Rozek’s chart, which Merck displayed at trial, plotted “new prescriptions” for Fosamax. The chart is accurate, but the inferences Merck draws from it are not. Dr. Rozek was not attempting to use a plot of “new prescriptions” as a visual guide to sales growth. As Dr. Vellturo admitted, to prepare such a plot, the data must first be corrected for switching from daily to weekly, because a “new prescription” that merely represents a patient changing from daily to weekly Fosamax cannot be a measure of the incremental success

of the once-weekly invention. (Vellturo 780-81 and 800). In fact, Dr. Vellturo included a “switching” correction in his analysis (*see, e.g.*, DTX543), as did Dr. Rozek in other of his visual summaries (*see, e.g.*, DTX540), and these plots do not demonstrate a sharp increase in new prescriptions with the introduction of once-weekly Fosamax. The bottom line with respect to sales, however, is Merck’s admission that the once-weekly product did not create new growth trends; instead, it merely continued the strong growth of Fosamax. (DTX355 at 4).

It was Merck’s burden to show the relevance of “commercial success” to this case, to show that the “commercial success” actually occurred, and to show that any “commercial success” was connected to the advantages of the patented invention. Merck failed to show any of them.

CONCLUSION

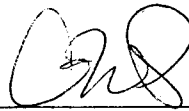
For the reasons set forth herein and in Teva's Opening Brief and Proposed Findings of Fact and Conclusions of Law, claims 23 and 37 of the '329 patent are invalid and unenforceable.

Respectfully submitted,

YOUNG, CONAWAY, STARGATT &
TAYLOR LLP

April 11, 2003

By



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CERTIFICATE OF SERVICE

I, Adam W. Poff, Esquire, hereby certify that I caused copies of the foregoing document to be served on April 11, 2003 upon the following counsel of record in the manner indicated:

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A handwritten signature in black ink, appearing to read 'GWP', is positioned above a horizontal line.

Adam W. Poff

EXHIBIT F

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- than an angle normal to the surface being inspected.
15. The Magistrate Judge's construction of "plurality of scan path segments" is not adopted. "Plurality of scan path segments" means more than one distinct scan segment. The Court otherwise adopts the reasoning of the Magistrate Judge.
 16. The Magistrate Judge's construction of "gallery definition means" is adopted with modification. "Gallery definition means" is supported by the structure of conventional computer hardware and software with the function of determining what items may be displayed by the "gallery display means" of the claims.
 17. KLA's motion for partial summary judgment of the '259 patent for obviousness (D.I. 584) is denied.
 18. ADE's cross-motion of non-obviousness of the '259 patent (D.I. 602) is denied.
 19. KLA's motion for partial summary judgment of invalidity of the '259 patent under 35 U.S.C. § 112, ¶ 1 (D.I. 587) is denied.
 20. KLA's motion for partial summary judgment of non-infringement of the '259 patent by KLA's SP1-TBI device (D.I. 566) is granted, as KLA's SP1-TBI device does not satisfy the "oblique zone" limitation.
 21. KLA's motion for partial summary judgment of non-infringement of the '259 patent by KLA's SP1-TBI and SP1-DLS devices (D.I. 590) is moot as to the SP1-TBI device and denied as to the SP1-DLS device.
 22. The Magistrate Judge's finding that KLA's motion for partial sum-

mary judgment of non-willful infringement of the '525 patent (D.I. 249) is moot is adopted by the Court.

23. The Magistrate Judge's finding that KLA's motion to dismiss ADE's claims of willful infringement of the '525 and '259 patents (D.I. 253) is moot as to the '525 patent is adopted. As to the '259 patent, the motion (D.I. 253) is denied.



MERCK & CO., INC., Plaintiff,

v.

**TEVA PHARMACEUTICALS
 USA, INC. Defendant.**

No. CIV.A.01-048-JJF.

United States District Court,
 D. Delaware.

Aug. 28, 2003.

As Amended Jan. 7, 2004.

Patentee brought infringement action against competitor, alleging that its patent for an osteoporosis drug was infringed by competitor's proposed generic drug. The District Court, Farnan, J., held that: (1) determination of British court that European drug patent was invalid as obvious was not entitled to collateral estoppel effect; (2) claims in patent referring to dosage of "about 70/35 mg" of alendronic acid meant equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances; (3) newsletter article did not anticipate patent; (4) patent was not invalid as obvious; and (5) patentee's fail-

ure to disclose newsletter article during application was not inequitable conduct.

Ordered accordingly.

1. Judgment ⇨713(1)

Collateral estoppel is appropriate if: (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) plaintiff had a full and fair opportunity to litigate the issue in the first action.

2. Patents ⇨327(13)

Doctrine of collateral estoppel applies in patent cases.

3. Patents ⇨327(21)

Determination of British court that European drug patent was invalid as obvious was not entitled to collateral estoppel effect in action for infringement on the United States patent; standards for determining obviousness in the United States and Britain were different, and British court's factual findings relating to obviousness were not essential to its decision.

4. Patents ⇨112.5

The party challenging the patent bears the burden of proving by clear and convincing evidence that the patent is invalid. 35 U.S.C.A. § 282.

5. Patents ⇨112.5

Clear and convincing evidence necessary to establish a patent's invalidity is evidence that places in the fact finder an abiding conviction that the truth of the factual contentions are highly probable. 35 U.S.C.A. § 282.

6. Patents ⇨314(5)

The first step in any patent invalidity analysis is claim construction, which is an issue of law.

7. Patents ⇨161

A patent claim term should be construed to mean what one of ordinary skill in the art at the time of the invention would have understood the term to mean.

8. Patents ⇨157(2)

When conducting a patent claim construction analysis, a district court should be cognizant of the fact that claims should be construed, if possible, to uphold their validity.

9. Patents ⇨165(1), 167(1), 168(2.1)

The starting point for a patent claim construction analysis is the claims themselves; then remainder of the intrinsic evidence should be examined, beginning with the specification and concluding with the prosecution history.

10. Patents ⇨161, 162

Generally, there is a strong presumption in favor of the ordinary meaning of claim language as understood by those of ordinary skill in the art; however, a patentee may act as his own lexicographer and use the specification to supply implicit or explicit meanings for claim terms.

11. Patents ⇨162

The patentee's lexicography must, appear with reasonable clarity, deliberateness, and precision before it can affect the claim.

12. Patents ⇨159

If the meaning of a patent claim term is clear from the totality of the intrinsic evidence, than the claim may be construed; if, however, the meaning of a claim term is genuinely ambiguous after examining the intrinsic evidence, than a court may consult extrinsic evidence.

13. Patents ⇨101(2)

Claims in patent for osteoporosis drug, referring to dosage of "about 70/35

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mg” of alendronic acid, meant equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carried accessories; term “about” did not mean “approximately,” since patentee explicitly defined term so that tablets contained the same number of core molecules as 70/35 mg of alendronic acid regardless of the final weight of the actual active ingredient in tablet.

14. Patents ⇌72(1)

Anticipation is determined through a comparison of the patent claim language with a single prior art reference. 35 U.S.C.A. § 102(e)(2).

15. Patents ⇌72(1)

Anticipation requires that every element of the patent claim be found either expressly or inherently in a single prior art reference. 35 U.S.C.A. § 102(e).

16. Patents ⇌68

If the prior art reference does not expressly state an element of patent claim, that reference may still anticipate if that element is inherent in its disclosure; inherency is established if the evidence makes clear that the missing descriptive matter is necessarily present in the thing described in the reference and, and that it would be so recognized by persons of ordinary skill. 35 U.S.C.A. § 102(e).

17. Patents ⇌68

Although inherency cannot be established through probabilities, recognition by a person of ordinary skill in the art before the critical date of the patent is not required to show inherent anticipation. 35 U.S.C.A. § 102(e).

18. Patents ⇌70

Newsletter article referencing weekly 40 or 80 mg dose of oral alendronate for treatment of osteoporosis did not anticipate patent for osteoporosis drug, which

expressly disclosed weekly doses of “about 35 mg” and “about 70 mg” of alendronate sodium “on an alendronic acid basis,” absent evidence that the dosages referred to in the article and the dosages referred to in the patent were equivalent. 35 U.S.C.A. § 102(e).

19. Patents ⇌16(2, 3), 36.1(1), 36.2(1)

The underlying factual inquiries in obviousness determination require consideration of: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any secondary considerations of nonobviousness such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid. 35 U.S.C.A. § 103.

20. Patents ⇌36(2)

As with anticipation, the burden of demonstrating obviousness of patent is with the challenger and invalidity must be proven by clear and convincing evidence. 35 U.S.C.A. § 103.

21. Patents ⇌16.25

Patent for osteoporosis drug, which expressly disclosed weekly doses of “about 35 mg” and “about 70 mg” of alendronate sodium, was not invalid as obvious, despite prior newsletter article that disclosed weekly 40 or 80 mg dose of oral alendronate for treatment of osteoporosis; newsletter article did not overcome the serious side effect concerns associated with the higher dosage levels it described, and weekly dosing regimen described in patent was commercially successful. 35 U.S.C.A. § 103.

22. Patents ⇌26(1)

In order to establish obviousness from a combination of elements disclosed in prior art, there must be some motivation,

suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. 35 U.S.C.A. § 103.

23. Patents ⇨97

Duty of candor, good faith, and honesty imposed on patent applicants and their patent attorneys includes the duty to submit truthful information and the duty to disclose to the Patent and Trademark Office (PTO) information known to the patent applicants or their attorneys which is material to the examination of the patent application. 37 C.F.R. § 1.56(a).

24. Patents ⇨97

Breach of the duty of candor, good faith, and honesty by patent applicant or patent attorney may constitute inequitable conduct. 37 C.F.R. § 1.56(a).

25. Patents ⇨97

If it is established that a patent applicant engaged in inequitable conduct before the Patent and Trademark Office (PTO), the entire patent application so procured is rendered unenforceable. 37 C.F.R. § 1.56(a).

26. Patents ⇨97

A patent applicant engages in inequitable conduct before the Patent and Trademark Office (PTO) when he withholds or misrepresents information material to the patentability of his invention, with an intent to deceive. 37 C.F.R. § 1.56(a).

27. Patents ⇨97

Inequitable conduct by patent applicant encompasses affirmative misrepresentations of material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive. 37 C.F.R. § 1.56(a).

28. Patents ⇨97

A reference withheld from patent application is considered material if there is a

substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. 37 C.F.R. § 1.56(a).

29. Patents ⇨97

After determining if patent applicant withheld information that is material, the court must then determine whether the evidence demonstrates a threshold level of intent to mislead the Patent and Trademark Office (PTO) in determining if patent is invalid because of inequitable conduct.

30. Patents ⇨97

Once materiality and intent to deceive Patent and Trademark Office (PTO) are established, the court should then weigh the findings and their premises and determine, in its discretion, whether to hold the patent unenforceable because of inequitable conduct. 37 C.F.R. § 1.56(a).

31. Patents ⇨97

Applicant's failure to disclose newsletter article that disclosed weekly 40 or 80 mg dose of oral alendronate for treatment of osteoporosis when applying for patent that disclosed weekly doses of "about 35 mg" and "about 70 mg" of alendronate sodium to treat osteoporosis was not inequitable conduct that rendered patent invalid; article did not reflect the claimed invention directly and did not render the claimed invention invalid as either obvious or anticipated, and evidence failed to establish intent to deceive. 37 C.F.R. § 1.56(a).

32. Patents ⇨97

In a case involving an omission of a material reference to the Patent and Trademark Office (PTO), there must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known reference to establish inequitable conduct. 37 C.F.R. § 1.56(a).

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Patents ⇄ 328(2)

4,621,077. Cited.

Patents ⇄ 328(2)

5,994,329. Valid.

Mary B. Graham and Maryellen Noreika, Esquires of Morris, Nichols, Arsht & Tunnell, Wilmington, DE. Of Counsel: John F. Lynch, Nicolas G. Barzoukas, and Stephen E. Edwards, Esquires of Howrey Simon Arnold & White, LLP, Houston, TX. Paul D. Matukaitis, Edward W. Murray, and Gerard M. Devlin, Jr. Esquires of Merck & Co., Whitehouse Station, NJ, for Plaintiff.

Josy W. Ingersoll, and Adam W. Poff Esquires of Young, Conaway Stargatt & Taylor, LLP, Wilmington, DE. Of Counsel: James Galbraith, Maria Luisa Palmese and William G. James, II, Esquires of Kenyon & Kenyon, New York City, for Defendant Teva Pharmaceuticals, USA, Inc.

OPINION

FARNAN, District Judge.

I. Procedural Background

Plaintiff, Merck & Co., Inc. (“Merck”) is a Delaware corporation with its principal place of business in New Jersey. Defendant, Teva Pharmaceuticals USA, Inc. (“Teva”) is a New Jersey corporation with its principal place of business in Pennsylvania. Merck is the owner of the entire right, title and interest in United States Patent No. 5,994,329, entitled “Method for Inhibiting Bone Resorption” (the “’329 Patent”), which issued November 30, 1999, naming as inventors Anastasia G. Daifotis, Arthur C. Santora II, and John Yates. Merck filed the application for the ’329 Patent on July 22, 1997. The ’329 Patent

is set to expire on August 14, 2018. (PTX 1).

Merck listed the ’329 Patent in the Federal Drug Administration’s (“FDA”) publication “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”) in connection with its 70 mg and 35 mg dosage for alendronate sodium, which Merck markets under the name “Fosamax.” On October 3, 2000, Teva filed a supplement to an existing Abbreviated New Drug Application (“ANDA”) seeking FDA approval to market generic versions of Merck’s 70 mg alendronate sodium product for weekly administration. Included with Teva’s ANDA filing were “paragraph IV” certifications (21 U.S.C. § 355(j)(2)(A)(vii)(IV)) asserting that the Patents listed in the Orange Book, including the ’329 Patent, are invalid, unenforceable or would not be infringed by the commercial marketing of Teva’s proposed product. Merck filed this action on January 21, 2001, alleging that Teva’s filing of its supplement was an act of infringement under 35 U.S.C. § 271(e)(2)(A). Thereafter, Merck listed U.S. Patent No. 6,225,294 (the “’294 Patent”) in the Orange book and Teva filed a paragraph IV certification asserting that the ’294 Patent is invalid, unenforceable or would not be infringed by the commercial marketing of Teva’s proposed 70 mg alendronate sodium product. On October 4, 2001, Merck filed Civil Action No. 01-675-JJF, alleging that Teva’s filing of its supplemental ANDA was an act of infringement of the ’294 Patent under 35 U.S.C. § 271(e)(2)(A).

Subsequently, Teva filed another supplement to its ANDA, seeking approval to market a generic version of Merck’s 35 mg Fosamax product. The supplement also included a paragraph IV certification asserting that all the listed patents were invalid, unenforceable or would not be infringed by Teva’s commercial marketing of its proposed product. On November 6,

2001, Merck filed Civil Action No. 01-728, alleging that the filing of Teva's supplement to the ANDA was an act of infringement under 35 U.S.C. § 271(e)(2)(A). On January 14, 2002, the Court consolidated all three cases under Civil Action No. 01-048.

One of the listed patents against which Teva certified was U.S. Patent No. 4,621,077 ("the '077 Patent"), which had already been the subject of litigation between the parties in this Court (Civil Action No. 00-035-JJF) in connection with Teva's application to market alendronate sodium for daily administration. The Court entered judgment in favor of Merck in that case on December 2, 2002, and an appeal from that judgment is now pending in the United States Court of Appeals for the Federal Circuit. (D.I.123-1). The parties agreed that they will be bound in this case, with regard to issues concerning the '077 Patent, by a final decision in the prior litigation. (D.I.128). Prior to trial Merck stipulated that the only claims at issue in this litigation are claims 23 and 37 of the '329 Patent and further stipulated that it would not allege an invention date for those claims prior to July 22, 1997. (D.I.128).

Teva stipulated that if found valid and enforceable, claims 23 and 37 of the '329 Patent would be infringed by the commercial marketing of Teva's proposed 70 mg and 35 mg alendronate sodium products for weekly administration. (D.I. 109, Pre-trial Order, Tab 1, ¶¶ 8-9). The issues of validity and enforceability of the '329 Patent were tried before the Court from March 4-7, 2003.

The Court has jurisdiction over the parties and the subject matter pursuant to 28 U.S.C. § 1338(a). Additionally, venue is appropriate under 28 U.S.C. § 1391(c) and

§ 1400(b). Neither jurisdiction nor venue are contested by the parties. This Opinion constitutes the Court's Findings of Fact and Conclusions of Law with respect to the issues tried before the Court.

II. The '329 Patent and Bone Biology In General

The '329 Patent discloses less-frequent-than daily administration of bisphosphonates (*e.g.*, alendronate) to inhibit bone resorption. (D.I. 143 at 8). Claims 23 and 37, the only asserted claims, relate specifically to the treatment and prevention of osteoporosis by once-weekly administration of alendronate. Osteoporosis is related to processes that are imbalanced in bone, and therefore, the Court will discuss the background of bone biology as it relates to osteoporosis and the use of alendronate for treatment of the disease.

Bone is the tissue that provides mechanical support to the body. It is made up of a protein matrix, which is overlaid with mineral to give it hardness. (Russell¹ at 108-109; DTX 523 at 2). Two principal types of cells maintain bone: 1) osteoclasts, which break down bone, and 2) osteoblasts, which build new bone. *Id.* The process of bone destruction and rebuilding is known as "remodeling." In the bone remodeling process, osteoclasts attach to the bone surface, become activated, and erode away the bone material beneath them, leaving defects in the bone structure. The destruction of bone by osteoclasts is called bone "resorption." Osteoblasts then attach to the eroded surface of these defects, lay down new bone, and then become inactive. In the normal healthy adult the remodeling process is balanced. In other words, bone is destroyed and

1. The bench trial transcript is cited throughout the Opinion by a notation to the witness

and the page number of the transcript.

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built at the same rate. (Russell at 109–110; DTX 523 at 3–4).

In osteoporosis, bone destruction and formation are no longer balanced and bone is destroyed faster than it is replaced. Therefore, osteoporosis can lead to bone that is thinner, weaker, more fragile and porous. (Russell at 110–115; DTX 523 at 7, 8). Osteoporosis is treated primarily by inhibiting bone resorption—thus restoring the balance between bone destruction and formation. Alendronate inhibits bone resorption by blocking the bone destroying effects of osteoclasts. (Russell at 116–117). A small portion of the ingested drug makes its way to and adheres to the bone surface, where it resides until it is taken up by osteoclasts. The alendronate then inhibits the osteoclasts from resorbing bone. (Russell at 121–122; DTX 523 at 10).

Paget's disease is also a common bone disease characterized by increased bone resorption. In Paget's disease, increased bone remodeling occurs in localized areas of the skeleton. If Paget's disease is not detected and treated early it can lead to an increase in bone size, fractures, and deformity. (Russell at 97). Like osteoporosis, Paget's disease is treated by inhibiting bone resorption with alendronate. (Russell at 125–126).

III. Teva's Motion in Limine to Preclude Merck From Relitigating the Factual Findings Underlying the Decision in *Teva Pharmaceuticals Ltd. et al. v. Istituto Gentili Spa et al.* (D.I.113).

Teva filed a Motion in Limine to Preclude Merck from Relitigating the Factual Findings Underlying the Decision in *Teva Pharmaceuticals Ltd et al. Istituto Gentili Spa et al.*, (High Court of Justice,

Chancery Division, Patents Court, January 21, 2003)). (D.I.113). Accordingly, the Court will discuss the motion in limine before it delves into the issues of validity and enforceability of the '329 Patent.

Teva's principal defense in this case is that claims 23 and 37 are invalid because the claimed invention is anticipated or would have been obvious in view of the prior art. At the same time that the parties were litigating the validity of the '329 Patent in this Court, they were also involved in a case in the British High Court of Justice (the "High Court"). That case was a challenge by Teva and others to the validity of the European Patent No. 998,292 (the "'292 Patent"), which corresponds to the '329 Patent, and is based on the same provisional applications filed in July 1997. Teva, by its motion, contends that the '292 Patent covers the identical concept as the '329 Patent: the once-weekly dosing of alendronate sodium to treat osteoporosis, using seven times the normal daily dose.²

The High Court conducted a full trial on the merits from November 5–8, 2002, and heard further arguments from counsel on November 12–13, 2002. The trial involved live testimony from Merck's expert Dr. Socrates Papapoulos, who is Merck's expert in this case. In addition, Merck offered the testimony of Dr. Yates, the principal inventor of the '329 Patent, who also testified in this case. On January 22, 2003, Justice Jacob of the High Court found that the claimed invention was invalid because it would have been obvious to a person skilled in the art, it claims a method of treatment, and is incapable of industrial application.

2. This claim is in the form of a "Swiss claim." Such claims are used in attempts to avoid restrictions on claiming methods of treat-

ment, which are unpatentable in many countries.

A. Applicable Legal Principles

[1,2] Teva contends that the Court should adopt the High Court's factual findings concerning obviousness pursuant to the doctrine of collateral estoppel. Collateral estoppel is appropriate if: (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) plaintiff had a full and fair opportunity to litigate the issue in the first action. *Micron Technology, Inc. v. Rambus, Inc.*, 189 F.Supp.2d 201, 209 (D.Del.2002) (citations omitted). Additionally, the doctrine of collateral estoppel applies in patent cases. *See Blonder-Tongue Laboratories, Inc. v. University of Illinois Foundation*, 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

B. Parties' Contentions

1. Teva's Contentions

By its motion, Teva contends that Merck had the identical motivation in litigating the British case as it does in the instant case: to discredit the *Lunar News* (a prior art reference) and Teva's reliance on its teachings. Moreover, Teva contends that Merck's barristers were afforded a full and fair opportunity to cross-examine all of Teva's witnesses and did so at length. Teva contends that the evidence was heard by Justice Jacob of the High Court, who is experienced in patents.

On January 22, 2003, Justice Jacob found the '292 Patent invalid and entered judgment against Merck. In its motion, Teva concedes that the legal standard may vary between Britain and the United States; nevertheless, Teva contends that regardless of the differences, if any, between the legal standards for determining validity, collateral estoppel should still apply to the resolution of the underlying factual issues. Specifically, Teva contends

that all of the elements of collateral estoppel are met in this case with regard to the High Court's factual findings on obviousness.

First, Teva contends that collateral estoppel applies to fact findings of foreign courts. Teva argues that courts have recently recognized that parties who litigate in a foreign court should be bound by the results of that litigation to the extent that the requirements of the collateral estoppel doctrine are met. For example, Teva points to *Vas-Cath, Inc. v. Mahurkar*, 745 F.Supp. 517 (N.D.Ill.1990), *rev'd on other grounds*, 935 F.2d 1555 (Fed.Cir.1991), where the parties extensively litigated the issue of obviousness in Canada, and the district court held that the parties were bound by the fact-finding of the Canadian Court. Additionally, Teva points to *Northlake Marketing & Supply, Inc. v. Glaverbel, S.A.*, 958 F.Supp. 373, 379 (N.D.Ill.1997) ("*Northlake I*") and *Northlake Marketing & Supply, Inc. v. Glaverbel, S.A.*, 986 F.Supp. 471, 475-76 (N.D.Ill.1997) ("*Northlake II*"), where the parties had previously litigated the validity of a Belgian patent that corresponded to the United States patent in suit. The district court in those cases held that the Belgian Court's conclusions about the scope and content of prior art were binding on the parties in the United States litigation.

Further, Teva directs the Court to *On-eac Corp. v. Raychem Corp.*, 20 F.Supp.2d 1233, 1242-1243 (N.D.Ill.1998), where a corresponding European patent was litigated in the High Court and the district court held that with respect to the United States patent, it would not give preclusive effect to questions of law or mixed questions of law and fact, but it would adopt the British Court's factual findings. Additionally, Teva points to Federal Circuit decisions that have declined to afford col-

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lateral estoppel effects to judgments in foreign cases, but distinguishes them on the basis that those decisions were predicated on what the Federal Circuit views as different standards of patentability in other countries. *See, e.g., Medtronic Inc. v. Daig Corp.*, 789 F.2d 903 (Fed.Cir.1986)(declining to adopt German tribunal's determination that corresponding German patent was invalid in view of different legal standards); *In re Dulberg*, 472 F.2d 1394 (Cust. & Pat.App.1973) (same).

Second, Teva contends that the issues were the same in the British litigation; the obviousness of administering alendronate sodium once a week at a dose of about seven times the daily dose. Further, Teva argues that the issue of the scope and content of the prior art are the same in both cases; whether the *Lunar News* publications taught the administration of alendronate sodium once a week, and whether the prior art taught that the dose should approximate seven times the daily dose. In addition, Teva argues that Merck's fear defense is an issue in both cases. Merck claims that persons skilled in the art would have rejected the *Lunar News* teachings because of the fear that patients would not tolerate the larger dose. Merck raised the issue in Britain, and after considering the evidence, the High Court concluded that the "fear defense fails". For example, the High Court found that the rare instances of esophageal side effects were attributed primarily to failure to follow the dosing instructions (D.I.114, Ex. A, ¶ 65).

Third, Teva argues that the same issues were actually litigated in the High Court. For instance, Teva contends, the parties fully aired all factual evidence, where both sides had qualified expert witnesses to explain the evidence to the Court. Further, Teva argues that all witnesses appeared live and were extensively cross-examined

and after the trial both parties provided written submissions and appeared for extensive argument before Justice Jacob. As a result, Teva argues, Merck cannot contend that these issues were not litigated.

Fourth, Teva argues that the issues were determined by a valid and final judgment. Teva points out that the judgment of the High Court was the "Approved Judgement of that Court." It was issued on January 21, 2003 and reissued in corrected form January 22, 2003. Teva notes that Merck has appealed the judgment, but that fact does not imply that the judgment is not final for purposes of collateral estoppel. In fact, Teva argues that it is well settled that the pendency of an appeal does not diminish the preclusive effect of an appealed judgment. (D.I. 114 at 13) (quoting *Rice v. Department of Treasury*, 998 F.2d 997, 999 (Fed.Cir.1993)).

Lastly, Teva contends that the resolution of obviousness was essential to the judgment in the High Court. Specifically, it contends that Justice Jacobs was required to and did evaluate and interpret the prior art provided by Merck's witnesses, and that, all findings on these issues were necessary to his final judgment that the patent was invalid for obviousness. Based on this, Teva argues that the High Court's factual findings should be given preclusive effect.

2. Merck's Contentions

In response, Merck argues that there is no transnational collateral estoppel as to the validity of a United States Patent. First, Merck contends that Teva fails to point to a single Federal Circuit case where, a foreign court's judgment that the patent was invalid, or the factual underpinnings of such a judgment, was given collateral estoppel effect in a case litigating the validity of a United States Patent. In fact,

Merck argues that the Federal Circuit and its predecessor court have rejected such attempts. For example in *Medtronic Inc. v. Daig Corp.*, 789 F.2d 903 (Fed.Cir.1986), *cert. denied*, 479 U.S. 931, 107 S.Ct. 402, 93 L.Ed.2d 355 (1986), the Federal Circuit rejected the argument that it should adopt the conclusion of a German tribunal that a German counterpart was obvious and stated, “[t]his argument is specious. The patent laws of the United States are the laws governing a determination of obviousness/nonobviousness of a United States patent in a federal court.” *Id.* at 907–908.

Additionally, Merck contends that the predecessor to the Federal Circuit came to the same conclusion in *In re Dulberg* 472 F.2d 1394, 1398 (Cust. & Pat.App.1973) and *In re Larsen*, 49 C.C.P.A. 711, 292 F.2d 531, 533 (Cust. & Pat.App.1961), where in both cases, the court refused to consider the actions of a foreign country’s patent office with respect to the patentability of the subject matter before the court.

Further, Merck argues that district courts have refused to give collateral estoppel effect to a foreign court’s judgment. For example, Merck points to *Cuno, Inc. v. Pall Corp.*, 729 F.Supp. 234 (E.D.N.Y. 1989), where the High Court found the European counterpart of the United States patent at issue to be valid and infringed, and when the plaintiff sought to have the United States district court give collateral estoppel effect to certain factual findings, the court denied the request and stated that:

Even if the court were to apply collateral estoppel to certain factual findings made by the British Court—as opposed to importing its legal conclusions wholesale—it is not clear that the trial time would be significantly shortened. Furthermore, the Federal Circuit’s reluctance to give collateral estoppel effect to

foreign judgments would seem to apply here to foreign findings of facts insofar as those findings involve mixed questions of fact and foreign law.

Id. at 238–239.

Moreover, Merck distinguishes the cases cited by Teva. First, in regard to the *Oneac* case, Merck points out that the court refused to give preclusive effect to questions of law or mixed questions of law and fact, and to the extent that certain factual findings were given collateral estoppel effect, it was because both parties to the suit agreed to be bound by those factual determinations. *Oneac Corp.*, 20 F.Supp.2d at 1242–1243. Additionally, Merck points to the *Vas-Cath* case where the Northern District of Illinois adopted certain factual findings of a Canadian Court in regard to the validity of a patent, after parsing out the Canadian judgment, comparing the relative Canadian and United States’ laws and making its own conclusions regarding the applicability of the factual determinations in the context of the United States’ legal framework. Additionally, in the *Northlake* cases, Merck points out that the district court adopted only certain factual findings from a previous Belgian proceeding after careful review of those findings and contends that most importantly, the issues that were precluded limited the evidence that the patent challenger could rely on. *See Northlake II*, 986 F.Supp. at 475–476; *Northlake I*, 958 F.Supp. at 379.

Next, Merck argues that the requirements for collateral estoppel have not been met. First, Merck contends that the High Court’s factual findings regarding obviousness were not essential to the final judgment because the High Court found that the ’292 was invalid based on three grounds: 1) invalid as a method of treatment; 2) incapable of industrial application; and 3) invalid as obvious—not obviousness alone.

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Lastly, Merck argues that the facts and applicable legal standard is different. Specifically, Merck contends that in the United States obviousness is ultimately a question of law which rests on the following factual inquiries: 1) the scope and content of prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) objective considerations of nonobviousness. *See Advanced Display Systems, Inc. v. Kent State Univ.*, 212 F.3d 1272, 1284–85 (Fed.Cir.2000). On the other hand, Merck argues, in Britain, the determination of obviousness is based on the following factual inquiries: 1) identifying the inventive concept embodied in the patent in suit; 2) assuming the mantle of the normally skilled but unimaginative addressee in the art at the priority date and impute to him what was, at that date, common general knowledge in the art; 3) identifying what, if any, differences exist between the matter cited as being made available to the public and the alleged invention; 4) determining whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they required any degree of invention. (D.I. 126 at 17) (citing *Windsurfing International, Inc. v. Tabur Marine (Great Britain) Ltd.*, 1985 R.P.C. 59, 60–61 (1985 Ct. Of Appeal)). Merck contends that although these standards are similar, the United States Court is required to consider objective considerations of obviousness, while in Britain they are not. Accordingly, Merck contends that collateral estoppel is improper.

C. Discussion

[3] As outlined above, the standards for determining obviousness in the United States and Britain are different. In fact, for purposes of this motion, Teva concedes that there may be differences in the legal

standards for validity between the United States and Britain. Additionally, after reviewing the “factual findings” of the High Court, the Court finds that many of the principles are mixed questions of law and fact. The cases cited demonstrate that mixed questions of law and fact should not be adopted if there are two different legal standards, as in this case. *See, e.g., Oneac Corp.*, 20 F.Supp.2d at 1242–1243 (declining to adopt mixed questions of law and fact). Additionally, in *Oneac* the court only adopted factual findings from a foreign tribunal where the parties agreed to be bound by such factual findings. *Id.* at 1242–43. This is not the situation in the instant case because Merck opposes any adoption of the High Court’s factual findings. Also, the Court finds that Merck has successfully distinguished the *Northlake* cases from the instant case, where in the *Northlake* cases the issues that were precluded limited the evidence that the patent challenger could rely on and the adopted factual findings did not go to the validity of the patent in suit.

The Court also concludes that all of the elements necessary for a finding of collateral estoppel are not present in this case. Specifically, the High Court’s factual findings relating to obviousness were not essential to the High Court’s decision because that decision was based on three separate grounds as detailed above. The Third Circuit has stated that “if a judgment of a court of first instance is based on determinations of two issues, either of which standing independently would be sufficient to support the result, the judgment is not conclusive with respect to either issue standing alone.” *Arab African Int’l Bank v. Epstein*, 958 F.2d 532, 535, (3d Cir.1992) (quoting Restatement (Second) of Judgments § 27, cmt. i), *rev’d in part on other grounds*, 10 F.3d 168 (3d Cir.1993). The Court concludes that based

on this standard, the High Court's finding of obviousness cannot be said to be essential to the final determination.

There may be cases where "the balance tips in favor of preclusion because of the fullness with which the issue was litigated and decided in the first action." *Masco Corp. v. United States*, 303 F.3d 1316, 1329–1330 (Fed.Cir.2002). However, the Court concludes that this is not such a case, especially in light of the fact that the Federal Circuit has cautioned courts against giving too much weight to foreign tribunals who are confronted with the same prior art. See *Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1072 (Fed.Cir.1994) (recognizing that theories and laws of patentability differ from country to country and stating that "[c]aution is required when applying the action of a foreign patent examiner to deciding whether the requirements of 35 U.S.C. § 103 are met under United States law, for international uniformity in theory and practice has not been achieved."). While the Court has reviewed Justice Jacob's factual findings in regard to obviousness, based on the aforementioned reasons, the Court declines to adopt them and will make independent findings of fact on the issue of validity. Accordingly, Teva's motion will be denied.

IV. Invalidity

[4, 5] Once issued a patent is presumed to be valid. See 35 U.S.C. § 282. The party challenging the patent bears the burden of proving by clear and convincing evidence that the patent is invalid. See *Helifix Ltd. v. Blok-Lok Ltd.*, 208 F.3d 1339, 1346 (Fed.Cir.2000). Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984).

Defendants contend that the '329 Patent is invalid and therefore cannot be infringed. Defendants argue invalidity on two grounds: anticipation by the July 1996 *Lunar News* reference under 35 U.S.C. § 102(a), and obviousness under 35 U.S.C. § 103. For the reasons set forth below, the Court concludes that the '329 Patent is valid.

A. Claim Construction

[6–8] The first step in any invalidity analysis is claim construction which is an issue of law. *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355 (Fed.Cir.2000); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970–71 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). A claim term should be construed to mean "what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *E.g.*, *Markman*, 52 F.3d at 986. Further, when conducting a claim construction analysis, a district court should be cognizant of the fact that claims should be construed, if possible, to uphold their validity. *In re Yamamoto*, 740 F.2d 1569, 1571 n. * (Fed. Cir.1984) (citations omitted).

[9] The starting point for a claim construction analysis is the claims themselves. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d at 1582; see also *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed.Cir.1999) (stating that "[t]he starting point for any claim construction must be the claims themselves."). Thereafter, the remainder of the intrinsic evidence should be examined beginning with the specification and concluding with the prosecution history. *Vitronics*, 90 F.3d at 1582 (outlining this order for examination in claim construction).

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[10, 11] Generally, there is a strong presumption in favor of the ordinary meaning of claim language as understood by those of ordinary skill in the art. *Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed.Cir.2001). However, it is well-settled that a patentee may act as his own lexicographer and use the specification to supply implicit or explicit meanings for claim terms. *Bell Atl. Network Servs.*, 262 F.3d at 1268 (Fed.Cir.2001); *Vitronics Corp.*, 90 F.3d at 1582; *Markman*, 52 F.3d at 980 (noting that patentee is free to be his own lexicographer, but emphasizing that any special definitions given to words must be clearly set forth in patent). “[T]he patentee’s lexicography must, appear ‘with reasonable clarity, deliberateness, and precision’ before it can affect the claim.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir.1998) (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed.Cir.1994)).

[12] If the meaning of a claim term is clear from the totality of the intrinsic evidence, than the claim may be construed. If, however, the meaning of a claim term is “genuinely ambiguous” after examining the intrinsic evidence, than a court may consult extrinsic evidence. *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed.Cir.1997).

Claim terms in claims 23 and 37 of the ’329 Patent are disputed in this case. Accordingly, the Court will focus its discussion on these claims

[13] In full, claim 23 of the ’329 Patent provides, “[a] method according to claim 22 wherein said unit dosage of said bisphosphonate comprises *about 70 mg* of alendronate monosodium trihydrate on an alendronic acid active basis.” (PTX 1, ’329 Patent at col. 21, lines 24–27) (emphasis added).

In full, claim 37 of the ’329 Patent provides, “[a] method according to claim 36 wherein said bisphosphonate unit dosage comprises *about 35 mg* of alendronate monosodium trihydrate, on an alendronic acid active basis.” (PTX 1, ’329 Patent at col. 22, lines 24–26) (emphasis added).

Teva contends that the term “about” in claims 23 and 37 should be construed according to its ordinary meaning of “approximately.” (D.I. 147 at 3). Merck contends that the patentee in this case acted as his own lexicographer and set out the meaning of “about” in the specification where the specification explains that the term “about” accounts for the variability of weight of the active ingredient that would result from the use of different salts of alendronic acids. (D.I. 141 at 42). Thus, Merck contends that the phrase “about 70 mg” as used in claim 23 and “about 35 mg” as used in claim 37 means 70 and 35 mg respectively of the active ingredient on an alendronic acid active basis. *Id.* at 43. In other words, Merck contends that, regardless of the final weight of the actual active ingredient in the tablet, it contains the same number of alendronate core molecules as 70/35 mg of alendronic acid.

In rebuttal, Teva contends that Merck’s proffered construction makes no sense. Teva points out that according to Merck, the word “about” is used to account for the fact that different alendronate salts have different molecular weights, and that to deliver the same amount of physiologically active compound to the bone they must be delivered at slightly different dosage strengths. (D.I. 147 at 4). Teva contends that Merck’s interpretation is nonsensical because the claim itself accounts for this phenomenon by directing that the compound be administered on the basis of a common denominator, *i.e.*, “on an alendronic acid active basis.” *Id.* In other words, Teva contends that the claims require that

the amount “alendronate sodium trihydrate” be sufficient to deliver the same amount of active material as “about 70/35 mg” of alendronic acid. *Id.* As a result, Teva contends, the term “about” does not perform the function which Merck assigns to it, and must be in the claim for another purpose, that is, to have its ordinary meaning of “approximately.”

After reviewing the claim terms and the specification, the Court concludes that the patentee explicitly and with reasonable clarity and precision defined the term “about 70 mg” in claim 23 and “about 35 mg” to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories. Simply put, no matter what the final weight of the actual active ingredient in the tablet is, it contains the same number of alendronate core molecules as 70/35 mg of alendronic acid.

The relevant portion of the '329 Patent specification provides:

Because of the mixed nomenclature currently in use by those or [sic] ordinary skill in the art, reference to a specific weight or percentage of bisphosphonate compound in the present invention is on an active weight basis unless otherwise indicated herein. For example the phrase “about 70 mg of bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof and mixtures thereof, on an alendronic acid weight basis” means that the amount of bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

PTX 1, the '329 Patent, col. 10, 65–col. 11, line 8. (emphasis added). The Court concludes that the specification clearly indicates that the terms “about 70 mg” and “about 35 mg” refer to the fact that de-

pending on the derivative of the alendronic acid that could be used in the oral formulation, different weights will be needed in order to get the same effect as 70 or 35 mg of the seminal compound, alendronic acid. As Merck points out, the alendronate sodium in Fosamax includes an atom of sodium metal for each molecule of alendronate sodium. (D.I. 138 at 24). If a formulator was to select a different salt which includes a metal atom that is heavier than salt, *e.g.*, a potassium or barium atom, the total amount of material in each tablet would have to increase if the amount of alendronic acid were to remain the same. By conforming the weight of the alendronate derivative in the claim of the '329 Patent to the equivalent weight of the alendronic acid, a formulator can consistently know how many basic units (alendronic acid units) are to be used, even though the final total weight may be different. Examples 7 and 8 of the '329 Patent reinforce this conclusion. They provide for oral formulations “containing about 35 mg” and “about 70 mg” of alendronate “on an alendronic acid active basis.” The claims at issue use the same phraseology and the ingredient tables in the examples are consistent with the premise that “about” accounts for the fact that alendronate derivatives have accessories that add to the weight of the molecules. Thus, in the examples “about 35 mg” turns out to be 45.68 mg of alendronate monosodium trihydrate and the “about 70 mg” turns out to be 91.35 mg of alendronate monosodium trihydrate. See PTX 1, the '329 Patent col. 19 lines 13–15, col. 19, lines 44–46, col. 19 lines 20–21, col. 19 lines 51–52.

Although the Court finds that Dr. Russell, is competent in the area of bisphosphonates, it does not find his opinion as to the definition of the phrases “about 70/35 mg” in the '329 Patent persuasive. During

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cross examination on this issue, Dr. Russell testified as follows:

Q. Now is it true that when you deal with the claims in this case, the claims recite 70 and 35; correct? That is 70 mg a week and 35?

A. The claims say about 70 and about

Q. And what does "about" mean to you?

A. Well about to me depends how precise a definition we want. But for purposes of how close the 40 and 80 are to about 35 and 70, I've given you my opinion on that, that for practical purposes, those would be the same, they would be indistinguishable in their effects, given everything else we know about the properties of these drugs.

Q. But the claim itself, what the claim really means, is 70, not 80; correct?

A. It says about 70 and about 35.

Q. Did you read the patent, Dr. Russell, the entire body of the patent?

A. Yes, I have.

Q. So in the patent, does it tell you what about 70 means?

A. There is a reference somewhere to about in the patent as I recall, but I'd need to be directed to where it was.

Q. Why don't you go to the first, in the patent, which is Defendant's Exhibit 1 and Plaintiff's Exhibit 1, at column 11, lines-about 1 through 9. It says here in the definitional context exactly what about 70 milligrams means; correct?

A. It well, there's almost an intrinsic contradiction in this, because the definition here is talking about 70, and then referring to whatever salt form is used being referenced to the alendronic acid itself, yes.

Q. But in the patent it gives you a precise reference and says when we say about 70 milligrams of a bone resorption

inhibiting bisphosphonate, what we mean is that amount of a bisphosphonate that will deliver an equivalent amount, the equivalent of 70 milligrams of alendronic acid; correct?

A. Yes. I have difficulty with this statement because the reason if it's that precise at 70, why does it use the phrase about?

Q. But they gave you that exact definition; correct?

A. *It's a curious use of the English language.*

Q. I understand, but it is what it says, and perhaps the person wanted to say if it's a certain salt one, you might use 71, and if it's a certain salt 2, you might use 73. Isn't that what's indicated in this?

A. Possibly.

Q. But that's what the definition says; right?

A. *That is the definition as it's described in the patent.*

Russell at 337-339. (emphasis added). Although Dr. Russell opined that the explicit definition of the disputed claim terms in the specification was "a curious use of the English Language," he testified that Merck's proffered construction is the definition as it is described in the patent. The Court finds Dr. Russell's interpretation unpersuasive, especially in light of the fact that patentees may give special meanings to claim terms either explicitly or implicitly in patent specifications. Further, with regard to Teva's claim that there is no function to Merck's proffered construction, the Court finds this argument unpersuasive given the clear directive in the specification to construe the term "about 70/35 mg" to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives and the fact that depending on the derivative of alendronic acid used in the

oral formulation, different weights will be needed in order to get the same effect as 70 or 35 mg of alendronic acid. *See Bell Atl. Network Servs.*, 262 F.3d at 1268 (noting that the specification must express a clear intent to redefine a claim term). Accordingly, the Court will accept Merck's proffered construction and construe the disputed claim terms "about 70/35 mg" to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories.

B. Anticipation

[14–17] Anticipation is determined through a comparison of the claim language with a single prior art reference. *See Wesley Jessen Corp. v. Bausch & Lomb, Inc.*, 209 F.Supp.2d 348, 391 (D.Del. 2002).

Anticipation under 35 U.S.C. § 102 requires that every element of the claim be found either expressly or inherently "in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed.Cir.1999). Thus, if the prior art reference does not expressly state an element of the claim, "that reference may still anticipate if that element is 'inherent' in its disclosure." *Id.* Inherency is established if the evidence makes "clear that the missing descriptive matter is necessarily present in the thing described in the reference and, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed.Cir. 1991). Although inherency cannot be established through probabilities, recognition by a person of ordinary skill in the art before the critical date of the patent is not

required to show inherent anticipation. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed.Cir.2003) (rejecting the contention that inherent anticipation requires recognition in the prior art before the critical date); *In re Robertson*, 169 F.3d at 745 (noting that inherent anticipation cannot be demonstrated through probabilities).

1. The Parties' Contentions

Teva contends that a July 1996 *Lunar News* article expressly anticipates claims 23 and 37 of the '329 Patent. Teva points out that since Merck has stipulated that it does not assert an invention date before July, 22, 1997, the July 1996 *Lunar News* is prior art under 35 U.S.C. § 102(a). (D.I. 143 at 19). Further, Teva points out that although it has the burden of proving invalidity by clear and convincing evidence, that burden is more easily met in this situation because Merck failed to provide the PTO with the July 1996 *Lunar News*.

Teva contends that the July 1996 *Lunar News* discloses every element of claims 23 and 37 of the '329 Patent. Teva points out that claim 23 defines a method of treating osteoporosis which comprises of oral administration of "about 70 mg" alendronate monosodium trihydrate, on an active alendronic acid basis, once-weekly. Similarly, Teva argues the July 1996 *Lunar News* discloses the same elements where it discusses the use of bisphosphonates, including alendronate, "in dealing with osteoporosis," which means the treatment and prevention of osteoporosis. (D.I. 143 at 21; Russell at 137). Further, Teva contends that the July 1996 *Lunar News* also specifies that the alendronate therapy it is

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discussing includes “oral” alendronate therapy, and that the term “alendronate” refers to “Fosamax by Merck.” Teva also contends that the active ingredient of Fosamax was well known to be alendronate monosodium trihydrate, and the dosage strength of Fosamax was known to be reported on an alendronic acid basis. (D.I. 143 at 21; DTX 394; Russell at 138–39). Teva also points out that the article specifies that the drug can be administered on a weekly basis at a dose of 80 mg where it states that, “. . . oral alendronate potentially could be given in a 40 or 80 mg dose once/week.” (D.I. 143 at 21)(quoting DTX 418 at 23). Teva directs the Court to Dr. Russell’s testimony where he opines that to a person skilled in the art, 80 mg of alendronate once per week is clinically indistinguishable from 70 mg once a week, and is therefore “about 70 mg.” (D.I. 143 at 21; Russell at 138). Teva also contends that Merck itself viewed 80 mg and 70 mg as the same weekly dose. (D.I. 143 at 21; DTX 147 at MK0158265). Thus, Teva contends the July 1996 *Lunar News* Article discloses every element of claim 23: treatment of osteoporosis by the administration of about 70 mg monosodium trihydrate on an alendronic acid basis once-weekly. (D.I. 143 at 22).

Teva further contends that the July 1996 *Lunar News* anticipates claim 37 of the ’329 Patent. Claim 37 claims a method for preventing osteoporosis in a human being comprising of orally administering about 35 mg of alendronate sodium on an alendronic acid basis as a unit dosage according to a continuous schedule having a dosage interval of once-weekly. (D.I. 143 at 22; DTX 1). Teva points out that the only difference between the two claims is that claim 23 is directed to “treatment” of osteoporosis with a 70 mg weekly dose, and claim 37 is directed to “prevention” with a 35 mg weekly dose. Teva reiterates the contention that the July 1996 *Lunar*

News deals with both the treatment and prevention of osteoporosis and discloses the use of a 40 mg once-weekly oral dose. (D.I. 143 at 22). Teva again directs the Court to Dr. Russell’s testimony where he testified that to a person skilled in the art, a 40 mg dose of alendronate once per week is clinically indistinguishable from 35 mg once per week and is therefore “about 35 mg.” (D.I. 143 at 22; Russell at 140; DTX 147 at MK0158265). As a result, Teva contends that the July 1996 *Lunar News* discloses every element of claim 37: prevention of osteoporosis by oral administration of about 35 mg alendronate monosodium trihydrate on an alendronic acid basis once weekly. (D.I. 143 at 22).

Teva contends that Merck’s “fear defense” is irrelevant to anticipation. First, Teva points out that claims 23 and 37 do not require that once-weekly administration of alendronate meet any standard of safety or tolerability. (D.I. 143 at 23). Even if they did, Teva argues, such a requirement would not avoid anticipation because the property of tolerability is inherent in the method disclosed in prior art. Further, Teva argues that the concept of “teaching away” from an invention is inapplicable in an anticipation analysis, and therefore, the Court should not consider it. (D.I. 143 at 24). Based on this, Teva contends that claims 23 and 37 are anticipated by the July 1996 *Lunar News*, and are therefore, invalid.

In reply, Merck contends that the July 1996 *Lunar News* fails to anticipate claims 23 and 37 of the ’329 Patent. Merck points out that the claims require the use of 70 or 35 mg of alendronate sodium on an *alendronic acid active basis* and even if one were to read the July 1996 *Lunar News* suggestion that “[e]ven alendronate potentially could be given in a 40 or 80 mg dose once/week” as referring to the amount on an alendronic acid active basis,

80 mg is not the same as 70 mg and 40 mg is not the same as 35 mg. Merck argues that the unambiguous weight requirement for alendronate in claims 23 and 37 is not met by the *Lunar News*' suggestion of 80 or 40 mg, and therefore, it fails to anticipate claims 23 and 37. (D.I. 138 at 27). Further, Merck argues that the July 1996 *Lunar News* is not enabling, and therefore, cannot anticipate. Specifically, Merck contends that in order for a disclosure to be enabling it must allow one of skill in the art to practice the invention, and the July 1996 *Lunar News* falls short of this standard because it fails to address the expectation by physicians in the field during 1996–1997 that alendronate sodium at doses over 20 mg would not be well-tolerated in the prevention and treatment of osteoporosis. Merck points to Dr. Fennerty's testimony to establish that a knowledgeable gastroenterologist during the applicable period would have been "extraordinarily concerned" about suggesting 40 or 80 mg of alendronate to treat osteoporosis. (D.I. 138 at 28; Fennerty at 270–271).

Further, Merck argues that Dr. Papapoulos, Merck's expert with extensive bisphosphonate and clinical osteoporosis experience, corroborates this sentiment. (D.I. 138 at 28). Merck argues that given the state of the medical knowledge at the time, a physician would not administer those high dosages when managing osteoporosis, and as a result, the July 1996

Lunar News fails to anticipate claims 23 and 37 of the '329 Patent.

2. Whether the July 1996 *Lunar News* Anticipates the '329 Patent

[18] After a review of the record evidence, the Court concludes that claims 23 and 37 of the '329 Patent are not anticipated under 35 U.S.C. § 102(a). Specifically, the Court concludes that Teva has failed to prove by clear and convincing evidence that the July 1996 *Lunar News* expressly or inherently discloses the dosage amounts for alendronate in claims 23 and 37. As a threshold matter and contrary to Teva's contentions, it has to prove invalidity by clear and convincing evidence. *See American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed.Cir.1984) (citations omitted) (stating that when a challenger produces prior art not before the PTO "the standard of proof does not change; it must be by clear and convincing evidence or its equivalent.") With this standard in mind, the Court will consider the parties' contentions with regard to anticipation.

The Lunar corporation was a manufacturer of bone densitometry equipment, which is a diagnostic tool for osteoporosis. (Russell at 129). The *Lunar News* was a quarterly newsletter distributed by the Lunar Corporation to its customers. (Mazess Dep. at 55–56; Russell at 129). It was authored by Dr. Richard Mazess¹, the former President of the Lunar Corporation. The July 1996 edition² contained a

1. Dr. Mazess does not possess an MD, has no formal training in pharmacology, and obtained his bachelors degree and Ph.D. in anthropology. (Mazess Dep. at 30–32).

2. The Court understands that Teva is not contending that the April 1996 edition of the *Lunar News* anticipates the '329 Patent. *See* D.I. 143, Opening Brief at 19–24 (failing to assert that the April 1996 *Lunar News* anticipates claims 23 and 37 of the '329 Patent).

However, even if Teva made this assertion, the Court concludes that the April 1996 *Lunar News* did not anticipate claims 23 and 37 because it does not suggest *any* dosage amounts in connection with its discussion of once-weekly dosing of alendronate. (DTX 417). Thus, it does not disclose all of the elements of claims 23 and 37, namely "about 35/70 mg" of alendronate, and therefore, cannot anticipate the claims either expressly or inherently.

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section entitled, "Update Bisphosphonate." (PTX 29 at 23). The section discusses bisphosphonates as a treatment for osteoporosis. *Id.* Specifically, in reference to the use of alendronate for treatment of osteoporosis, it states that "[s]ome United States physicians are reluctant to treat because of: a) side effects; b) difficulty of dosing; and (c) high costs (\$700/year)." (PTX 19 at 23). To address the difficulty of dosing and high costs the article suggests:

The difficulties with oral bisphosphonates may favor their episodic (once/week) or cyclical (one week each month) administration. Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

PTX 29 at 23. Teva contends that the July 1996 *Lunar News* article discloses all of the elements in claim 23 of the '329 Patent. Specifically, Teva argues that the July 1996 *Lunar News* discloses the following elements: 1) A method of treating osteoporosis in a human; 2) orally administering; 3) about 70 mg; 4) of alendronate monosodium trihydrate; 5) on an alendronic acid active basis; 6) as a unit dosage; and 7) according to a continuous schedule having a dosing interval once-weekly. (D.I. 143 at 23). Merck asserts that the July 1996 *Lunar News* article does not anticipate claim 23 because it fails to reference 70 mg of alendronate sodium on an alendronic acid active basis as required by claim 23. (D.I. 141 at 44).

After reviewing the July 1996 *Lunar News* in light of the '329 Patent, and the Court's construction of the claim terms, the Court is not persuaded that Teva has demonstrated by clear and convincing evidence that claims 23 and 37 of the '329 Patent are anticipated by the July 1996 *Lunar News*. The July 1996 *Lunar News* fails to reference 70 mg of alendronate

sodium *on an alendronic acid basis* as required by the claim. Instead it references an 80 mg dose of oral alendronate. Thus, it does not expressly disclose "about 70 mg" of alendronate sodium "on an alendronic acid basis." Likewise, the Court is not persuaded that Teva has demonstrated inherency. Although Dr. Russell testified that 80 mg and "about 70 mg" are the same for all practical purposes because they have the same effect on patients, he did not testify that this element was "necessarily present" in the July 1996 *Lunar News* reference or that its disclosure was sufficient to show that this element was the natural result flowing from the operation as taught. In fact, in the Court's view, Dr. Russell's testimony was insufficient on this issue, and was, at best, conclusory. For example, although Dr. Russell testified that 80 mg and 70 mg are the same for all practical purposes because they would have the same effect, the Court recognizes that in rendering his opinion Dr. Russell did not take into account the Court's construction of the term "about 70 mg". (Russell at 137-139). Further, the Court notes that Dr. Russell provided no evidence to support his conclusion that 70 and 80 mg were equivalent. In fact, Dr. Papapoulos testified on cross-examination that one would need to test the 80 and 70 mg doses before concluding with any certainty that they are the same and the regulations regarding the filing of an ANDA recognize that any change in the dosage of a drug would require additional data. (Papapoulos at 676-678; 21 U.S.C. § 355(j)(2); 21 C.F.R. § 314.93). Dr. Russell, provided no such data. Based on this, the Court concludes that Teva has failed to demonstrate that the July 1996 *Lunar News* inherently or expressly disclosed the element of "about 70 mg" of alendronate sodium "on an alendronic acid active basis" as required by claim 23 of the '329 Patent.

Similarly, the Court concludes that the July 1996 *Lunar News* fails to disclose “about 35 mg” as required by claim 37 of the ’329 Patent. Specifically, the July 1996 *Lunar News* fails to reference “35 mg” of alendronate sodium “on an alendronic acid active basis” as required by the claim. Although it references “40 mg”, in light of the Court’s claim construction of “about 35 mg” to mean the equivalent of 35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories, the Court concludes that the July 1996 *Lunar News* reference does not expressly disclose “about 35 mg” as required by claim 37. Likewise, the Court concludes that Teva’s inherency argument as to claim 37 must also fail. Dr. Russell testified that a 40 mg dose is about the same as a 35 mg for all practical purposes. (Russell art 140–141). However, the Court finds Dr. Russell’s opinion on this issue to be conclusory because he provides no evidence, statistical tests or data to support this assertion. Further, Dr. Russell did not testify that this element was “necessarily present” in the July 1996 *Lunar News* reference or that its disclosure was sufficient to show that this element was the natural result flowing from the operation as taught. Based on this, the Court finds that the evidence is insufficient to show that each element of claims 23 and 37 of the ’329 Patent were present in the prior art reference expressly or inherently. Accordingly, the Court concludes that Teva has failed to establish by clear and convincing evidence that the ’329 Patent was anticipated by the July 1996 *Lunar News*. Because the Court concludes that claims 23 and 37 of the ’329 Patent were not anticipated by the July 1996 *Lunar News*, the Court will not address the parties’ contentions concerning enablement of the prior art.

C. Obviousness

[19, 20] Teva contends that the ’329 Patent is invalid, under 35 U.S.C. § 103, as obvious. In pertinent part, 35 U.S.C. § 103 provides that a patent may not be obtained “if the differences between the subject matter sought to be patented and prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art . . .” 35 U.S.C. § 103. The obviousness determination is a question of law which is based on several underlying factual inquiries. See *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir. 1997). The underlying factual inquiries require consideration of the four “Graham” factors which are: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any secondary considerations of nonobviousness such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid. See *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1996). Additionally, as with anticipation, the burden of demonstrating obviousness is with the challenger and invalidity must be proven by clear and convincing evidence. *C.R. Bard, Inc. v. M3 Systems*, 157 F.3d 1340, 1351 (Fed.Cir.1998).

1. The Parties’ Contentions

Teva contends that the ’329 Patent is invalid as obvious because both the April 1996 and July 1996 editions of *Lunar News* explicitly disclose the weekly administration of alendronate for osteoporosis and a person skilled in the art would have understood in July 1997 that the weekly dose for treatment and prevention of osteoporosis should be “about 70 mg” and “about 35 mg” respectively, and that these

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doses are explicitly set out in the July 1996 *Lunar News*. Teva argues that not only did the *Lunar News* disclose the concept of once-weekly dosing and provide the appropriate dose, a person of ordinary skill would have predicted the *Lunar News* teaching to be effective. (D.I. 143 at 26).

Further, Teva contends that there was a motivation to employ once-weekly dosing because of the inconvenience of the dosing regimen which consisted of taking the tablet before eating, remaining upright for a half an hour and taking the tablet with a full glass of water. *Id.* at 27. Teva points out that the April 1996 and July 1996 editions of *Lunar News* explicitly stated the motivation to administer alendronate weekly; to improve patient convenience and compliance with the dosing instructions. *Id.* Thus, Teva argues that the prior art that claimed the invention also disclosed the motivation to make it. *Id.*

Teva contends that a person of skill in the art would not have been deterred from once-weekly dosing because of the fear of increased gastrointestinal side effects. *Id.* As to this point Teva argues that the early reports of esophagitis would not have deterred a person of skill in the art from once-weekly dosing because the early reports showed that these events were rare, occurring in one out of every ten thousand patients taking 10 mg of alendronate daily, and that these effects were for the most part reversible with proper treatment. *Id.* at 28; Markowitz at 436–37; 451. Teva also points out that in March 1996, five months after the launch of 10 mg daily alendronate tablet, ten million patients had been prescribed the tablet and fifty cases of severe esophagitis had been reported to Merck, and Merck took no action until it learned that a letter written by a well-known bone-specialist discussing two such cases was circulating within the Mayo

Clinic Health System. (D.I. 143 at 29; Hirsch Dep. at 54–56). When it finally took action, Teva argues, Merck’s investigation concluded that the pill esophagitis cases were caused primarily by the failure of patients to adhere to the dosing instructions. (D.I. 143 at 29; Markowitz at 442; Hirsch Dep. at 66; 82–84).

Teva also points out that in March 1996, Merck disseminated a “Dear Doctor” letter, informing physicians about the infrequent cases of esophagitis, stating that in a “large majority” of cases patients appeared to have not complied with the dosing instructions, and advocating “strict compliance” with those instructions. (D.I. 143 at 30; DTX 34). Merck later reported on the severe esophagitis cases in the October 1996 De Groen *et al.*³ article in the *New England Journal of Medicine*. (PTX 91). The De Groen paper reported that 51 patients experienced adverse effects classified as “serious” or “severe” out of the 470,000 patients worldwide who had received prescriptions for alendronate to treat osteoporosis up to that time. (D.I. 143 at 30). Teva directs the Court to its gastroenterology expert, Dr. David Markowitz, who testified that the extremely low incidence of these effects, and the description of the cases, led gastroenterologists to conclude at the time that the likely cause of the problem was “pill esophagitis.” (D.I. 143 at 30; Markowitz 435, 438). Teva argues that the evidence presented at trial leads to the conclusion that once-weekly administration would have been expected to decrease the incidence of severe esophagitis cases because it would: 1) improve patient compliance with the dosing instructions (Russell at 195–96; Markowitz at 485–86; Fennerty at 311); and 2) decrease the frequency of administration, thereby decreasing the chances of

3. De Groen *et al.*, *The New England Journal of*

Medicine, 1996 (PTX 91).

the tablet “sticking” in the esophagus (Russell at 196–197; Markowitz at 443).

Teva also asserts that the evidence presented at trial does not support a dose-response relationship between alendronate and gastrointestinal effects that would have deterred a person of ordinary skill in the art from once-weekly dosing. (D.I. 143 at 32). For example, Teva argues that the results of the Chestnut⁴ study related to daily and not weekly dosing and demonstrated that 90% of postmenopausal women with osteoporosis tolerated the 40 mg daily dose. *Id.* at 34. Also, Teva contends that Dr. Fennerty’s testimony regarding a dose-related relationship was discredited by Merck’s pre-litigation behavior and directs the Court to the testimony of Dr. Markowitz who testified that his contemporaneous investigations indicated that severe events were extremely rare with alendronate and that overall the drug was well tolerated. *Id.* at 35.

In addition, Teva contends that before this litigation, Merck admitted that prior art data available in July 1997 from Paget’s patients showed that once weekly dosing would be well-tolerated. For example, Teva directs the Court to a May 1997 “Tactical PAC” review seeking management approval to go forward with the once-weekly dosing program where it stated that “the 40 and 80 mg doses were well-tolerated even when given on a daily basis.” (D.I. 143 at 39, DTX 147 at MK0158265). Further, Teva points out that Merck, in a formal submission to the FDA maintained that data from Paget’s disease provided an expectation that once-weekly doses would be well tolerated. (D.I. 143 at 39; DTX 192 at 17).

Teva also argues that a person of skill in the art would not have been deterred from once-weekly dosing because of the alleged

dose-related effects of prior art bisphosphonates, because the magnitude of data available on alendronate in treating osteoporosis and Paget’s disease made reference to other bisphosphonates unnecessary. (D.I. 143 at 41). Teva also points out that Merck’s Physician Survey conducted in 1997 indicated that physicians perceived that larger less-frequent doses would result in “less-GI upset.” (D.I. 143 at 43; DTX 244 at MK0174861).

Teva also contends that the ’329 invention did not provide unexpected results because the prior art disclosed its principal advantage; convenience and compliance. (D.I. 143 at 44). Additionally, Teva contends that Merck did not carry its burden of demonstrating commercial success because it was required to show that the once-weekly product contributed to the incremental success beyond the daily product and that Merck’s expert, Dr. Vellturo failed to demonstrate any connection between the patented invention and Merck’s sales of once-weekly Fosamax. Specifically, Teva contends that Dr. Vellturo did not opine that the two were connected but merely asserted that “commercial success could be at least in part, significant part, attributable to the Daifotis patients.” D.I. 143 at 48; Vellturo at 715. Further, Teva suggests that Dr. Vellturo’s analysis is flawed because of his emphasis on sales and prescriptions as the only indicia of success without considering any other market factors such as the increased awareness about osteoporosis and the effect of the increasing number of Americans over the age of sixty, like its own expert, economist, Dr. Richard Rozek took into account. (D.I. 143 at 48). Additionally, with regard to commercial success, Teva contends that Merck ignored its own successful marketing efforts such as its heavy promotional expenditures during the appli-

4. Chestnut *et al.*, *The American Journal of Medicine*, 1995, (PTX 69).

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cable period when examining the commercial success of the once-weekly dose of alendronate. (D.I. 143 at 51). Finally, Teva argues that Dr. Velturo's diffusion model is flawed because a diffusion model is not particularly useful as a forecasting device, and therefore, its use in this context is inappropriate and alternatively argues that Dr. Velturo's use of the model is incorrect. (D.I. 143 at 54).

In response, Merck contends that the once-weekly high dose regimen of the '329 Patent was not obvious to a skilled practitioner in 1997 because without hindsight, the overwhelming knowledge in the field was that high oral unit doses would not be safe and tolerable for osteoporotic women. Merck points out that Dr. Russell, Teva's expert, acknowledged that a person of ordinary skill "would be familiar with publications in the field and the technical background in this field of bisphosphonates and osteoporosis." (Russell at 144). Thus, according to Dr. Russell's interpretation of one of ordinary skill, Merck argues, a skilled practitioner would know that: 1) etidronate and clodronate caused gastrointestinal side effects at high doses; 2) pamidronate caused dose-related gastrointestinal side effects that even led to the discontinuation of its development as an oral medication; 3) alendronate caused dose-related gastrointestinal side-effects; and 4) alendronate sodium, even though proven to be safe and tolerable at 10 and 5 mg doses, could still potentially cause severe upper gastrointestinal injuries. (D.I. 145 at 10-11) (citations omitted). Merck contends that the overwhelming knowledge, laid out by contemporaneous publications in respected peer-reviewed medical journals establishes that the pre-invention expectation by those skilled in the art was that one could not use alendronate sodium at unit doses higher than 20 mg for the management of osteoporosis. *Id.* at 11.

Further, Merck asserts that Teva's "spin" on the Chestnut study is flawed. Specifically, Merck points out that in the Chestnut study only one out of sixty two women (1.6%) withdrew from the 10 and 5 mg doses, but seven out of sixty three women (11.1 %) withdrew from the 40 mg alendronate treatment. *Id.*; PTX 69 at 150; Markowitz at 479-482; Fennerty at 266. Moreover, contrary to Teva's assertion, Merck points out that it informed the FDA that the Chestnut Study had led it to "limit the maximum dose to 20 mg in subsequent osteoporosis treatment studies." (D.I. 145 at 15; PTX 202 at MK250180; PFF 66). Additionally, Merck asserts that as Dr. Papapoulos testified, a skilled practitioner at the time knew that in actual clinical practice 10 to 12 percent of patients discontinued 10 mg Fosamax treatment because of gastrointestinal side effects. (D.I. 145 at 12; Papapoulos at 651-652). Thus, Merck argues that any reasonable clinician, viewing this data could compare these ratios and would expect the discontinuation rate for osteoporotic women in actual practice, outside the confines of a controlled clinical environment, to have been unacceptably high at a 40 mg dose. Merck asserts that Teva failed to consider that clinical studies are different than daily practice and that discontinuations are far less common in the context of a clinical study. (D.I. 145 at 12; PFF 60; Fennerty at 262-64).

In reference to Teva's reliance on internal and FDA submitted documents, Merck contends that these publications as presented by Teva were taken out of context, and therefore, do not bolster Teva's argument with regard to obviousness. Merck argues that Teva improperly relied on these documents because these documents reflect the inventors' rationales to overcome the skepticism about high unit doses and the inventors' insights about their own invention. In regard to extrapolating re-

sults from the Paget's disease experience to doses for osteoporosis, Merck points out that Professor Fleish's book, which Dr. Russell later edited, reflected the thinking in the art that the tolerability for alendronate sodium appeared to be higher for the Pagetic disease population than the osteoporosis population. (D.I. 145 at 15).

Merck also contends that it has never disputed that it was known that once-weekly dosing would be efficacious in providing the alendronate sodium needed to inhibit bone resorption, but notes that it was the safety concern about high oral doses (higher than 20 mg) that obscured the advantageous once-weekly invention for the management of osteoporosis. (D.I. 145 at 15). Further, Merck points out that it did not rely on the case reports such as *De Groen* as evidence of a dose-response, rather, Merck claims, the case reports simply raised the awareness of physicians that alendronate sodium was a potentially dangerous agent and that Teva's expert, Dr. Markowitz admitted that the case reports were clinically significant. (D.I. 145 at 18; Markowitz at 468). Merck also rebuts the contention that it took no action in response to the case reports and points out that it promptly obtained data about each case, constructed a data base and organized a meeting with Dr. De Groen and other consultants by March 1996. Then, on March 15, 1996 Merck sent out a "Dear Doctor" letter informing physicians about the potential upper gastrointestinal injuries and emphasizing the importance of following directions in order to minimize them. Merck also undertook internal studies to understand the problem, including dog studies. (D.I. 145 at 19; PTX 67; PFF 88).

In reference to Dr. Fennerty's testimony, Merck contends that Teva mischaracterized his testimony regarding the Blank⁵

article. Merck asserts that the Blank study provided a glimpse as to what happens when the use of aminobisphosphonates is combined with Non-Steroidal Anti-Inflammatory Drugs ("NSAIDs") such as aspirin and ibuprofen. This study was published during February of 1997 in the peer-reviewed *Digestive Diseases and Sciences*, and it showed clear dose-related upper gastrointestinal injuries from alendronate sodium when it was combined with the NSAID indomethacin in a rat model. (D.I. 145 at 20; PTX 104 at 284 fig. 3). Merck contends that Dr. Fennerty observed that when placed in the mosaic of prior art showing the dose dependent injuries from bisphosphonates, the Blank study was important to gastroenterologists, and he never retreated from this position. (Fennerty at 270, 292-94). Additionally, Merck points out that Teva itself stated to the PTO in 2000, in an attempt to gain the issuance of claims for a delayed gastric release alendronate formulation, that bisphosphonates as a class exhibit side effects that "consist of irritation of the upper gastrointestinal mucosa . . . with the potential for this irritation leading to more serious conditions." (PTX 301, U.S. Patent No. 6,476,006 ("the '006 Patent") at col.3, lines 25-25). Merck contends that Teva also told the PTO that the "larger" once weekly doses have "the potential of exacerbating the upper GI side effects of the drug." D.I. 145 at 21 (quoting the '006 Patent at col. 3, lines 12-14).

Merck argues that Teva's reliance on the 1997 Physicians Survey is misplaced because it did not address the use of higher doses. Specifically, Merck points out that at issue is the invention of administering seven-fold the daily dose of alendronate sodium once a week, and in the survey, a twice-weekly dosing schedule was

5. Blank *et al.*, *Digestive Diseases and Sciences*,

1997 (PTX 106).

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inquired about along with other choices that included placing alendronate sodium in diet colas and cranberry juice. (D.I. 145 at 22; DTX 244 at 174866). Merck points out that the invention of the '329 Patent does not lie solely in the less frequent dosing, but in the fact that an entire weekly complement of daily doses could be administered as a single unit dose and that the marketing survey inquired about twice weekly dosing without any mention of increasing the dose. Therefore, Merck argues that it does not bear any relevance to the invention of once-weekly dosing at sevenfold the daily dose. (D.I. 145 at 22).

In regard to secondary considerations, Merck contends that contrary to Teva's assertion that commercial success is irrelevant in the obviousness inquiry because Merck was the only entity allowed to market alendronate sodium tablets, its direct competitors, including Procter & Gamble, had an incentive to develop an improved dosage form. (D.I. 145 at 23). Further, in reference to commercial success, Merck contends that the increased sales for the Fosamax franchise upon the launch of the once-weekly dosing regimen is dramatic regardless of which way it is viewed. (D.I. 145 at 25). Specifically, Merck points out that the Fosamax franchise sales followed a constant increase trend from 1996 until the introduction of once-weekly Fosamax in 2000, where if the trend established before the once-weekly dose was introduced had continued, an increase of 18.9% over the prior year would have resulted. However, after the once-weekly dosing was introduced, a dramatic increase of 42.5% was realized. (D.I. 145 at 26; PTX 166; Velturo at 718-720). Additionally, Merck contends that Teva's attempt to discredit Dr. Velturo's diffusion model was unsuccessful. Merck argues that, in any event, Dr. Velturo testified that his opinion regarding the commercial success of the '329 Patent was not based on model,

but on a fundamental shift in the constant trends he observed regarding the Fosamax franchise's sales increases, market share, prescription volume and on an evaluation of the market share and prescription volume data for the osteoporosis market as a whole, and that the diffusion model only confirmed the opinion he formed based on the aforementioned factors. (D.I. 145 at 26; Velturo at 718-728, 735, 755-757). Finally, Merck notes that Dr. Rozek, Teva's expert on obviousness, provided no ultimate conclusion about the commercial success of the once-weekly dosing of Fosamax or any of the factors he believed Dr. Velturo should have considered. (D.I. 145 at 26).

2. Whether the '329 Patent Was Obvious in View of the Prior Art

[21, 22] After reviewing the relevant prior art in light of the evidence and the factors related to the obviousness inquiry, the Court concludes that Teva has failed to establish by clear and convincing evidence that the '329 Patent was obvious in light of the prior art references. The Court in its obviousness analysis must be cognizant of "hindsight syndrome." *In re Werner Kotzab*, 217 F.3d 1365, 1369-1370 (Fed.Cir. 2000). The Federal Circuit has instructed that, "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Gartside*, 203 F.3d 1305, 1319 (Fed.Cir.2000). Therefore, in order to establish obviousness from a combination of elements disclosed in prior art, "there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *Kotzab*, 217 F.3d at 1370. With this standard in mind, the Court will discuss the relevant

factors of the obviousness inquiry as they relate to the '329 Patent.

i. *Level of One Skilled in the Art*

For the purposes of the obviousness inquiry, the Court finds that at the time of the filing of the '329 Patent, a person of ordinary skill in the art was an individual who would have an M.D. and/or Ph.D. and was working in the field of and doing research on osteoporosis. Such a person would be familiar with the publications and technical literature and background in the field of bisphosphonates and osteoporosis. (D.I. 142 at 17–18; D.I. 141 at 41). The Court bases this finding on a combination of Merck and Teva's proffered interpretation of one skilled in the art and finds that there are no significant differences between the two proffered definitions.

ii. *Scope and Content of Prior Art*

At the outset, the Court notes that Merck has never disputed that it was known that once-weekly dosing would be efficacious in providing the alendronate sodium needed to inhibit bone resorption. (D.I. 145 at 15). However, Merck contends that it is the safety concern about high oral doses, specifically unit doses higher than 20 mg, that obscured the advantageous once-weekly invention for the management of osteoporosis. *Id.* Thus, the issue is when viewing the mosaic of the prior art, whether those of ordinary skill in the art would have had the motivation to formulate a once-weekly seven-fold daily dose of alendronate sodium, despite safety concerns.

The Court concludes that the history of bisphosphonates as a class is minimally relevant to the instant discussion because although alendronate is a bisphosphonate and general knowledge of bisphosphonates is certainly within the knowledge of one of ordinary skill in the art during the relevant time period, it was also well known

that each bisphosphonate had its own unique characteristics. (See DTX 547 at 543) (Dr. Papapoulos, Merck's expert, noting that because of differences in mechanisms of action and pharmacological and toxicological profiles, it is "important that specific properties of every individual bisphosphonate be determined and that results obtained with one bisphosphonate not be extrapolated readily to the whole class."). As a result, although the earlier bisphosphonates etidronate, clodronate and pamidronate had dose related gastrointestinal side effects, the Court concludes that this fact holds little weight in its obviousness analysis given the unique characteristics of each bisphosphonate, particularly with side effects. (Papapoulos at 653–654; Russell at 384–385; PTX 110 at 127, 129, 130; PTX 111 at 148, 149, 152; PTX 112 at 154, 15, 1585; PTX 113 at 170, 171, 175; PTX at 289, E91, C278, C279).

Therefore, the Court will focus its discussion on the prior art dealing with alendronate. The 1995, 1997, and 2000 editions of "Bisphosphonates in Bone Disease" written by Professor Herbert Fleish, who is described as the "father of bisphosphonates", reported that oral alendronate sodium can cause gastrointestinal disturbances at doses of 40 mg. (PTX 111 at 148; PTX 112 at 153; PTX 113 at 169; *see also* PTX 300 at 26). Further, in the 1997 and 2000 editions, Dr. Fleish reported that a 40 mg dose may cause gastrointestinal disturbances in patients with osteoporosis, but that the same dose was well tolerated in patients with Paget's disease. (PTX 112 at 153; PTX 113 at 169).

Additionally, the Court finds that case reports are probative in its obviousness inquiry because, as Dr. Fennerty testified, they often contain information that would alter the way a physician would treat patients. (Fennerty at 247–248). Case re-

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ports are publications usually involving one or a few patients that have an outcome of clinical relevance or importance. (Fennerty at 246–247). In October 1995, Maconi⁶ published a case report in the *American Journal of Gastroenterology*, which reported that an osteoporosis patient after taking 5 mg of alendronate, had an endoscopy which revealed severe damage to the esophagus. (Fennerty at 249–250). Dr. Fennerty testified that this case report was significant because the particular journal it was published in was “clinically relevant” and because this “severity of injury had never been reported in a patient taking a bisphosphonate prior to this, especially a bisphosphonate that was being used now very commonly in clinical practice as it had just been released at about the time the case report was published.” (Fennerty at 250). In October 1996, De Groen published an article in *The New England Journal of Medicine* which set out three case reports describing the side effects of alendronate sodium. (PTX 91). The first case report reported that a 73-year-old woman developed chest pain and dysphagia after her first dose of 10 mg of alendronate sodium. (PTX 91 at 1016–1017). After two more doses she was transferred to the Mayo Clinic where an endoscopy revealed severe ulcerative esophagitis. (PTX 91 at 1017; Fennerty at 254–56). The other two case reports revealed that two additional women developed severe esophageal injury as a result of taking 10 mg oral dose of alendronate sodium. (PTX 91 at 1017; Fennerty 254–256). The article also revealed that Merck revised dosing instructions in the Fosamax product circular based on the results noted in the paper so as to further minimize potential for prolonged contact of the drug with the esophagus and thus, to reduce the

risk of injury. (PTX 91 at 1020). Additional case reports published by Abdelmalek (PTX 96), Sorrentino (PTX 98), Naylor (PTX 101), Rimmer (PTX 102), Pizzanni (PTX 109) and Girelli (PTX 106) also suggested evidence that alendronate sodium may be associated with severe side effects not recognized in clinical trials. (Fennerty at 259).

The Court also finds that several studies dealing with alendronate are significant. In 1993, Harris⁷ published an early Phase II study, which is a dose-ranging study used to determine the dose and the preliminary data on both the safety and efficacy of a drug, sponsored by Merck in the *Journal of Clinical Endocrinology and Metabolism* investigating the effects of oral alendronate sodium treatment. (PTX 116; Russell at 159, 364–65). The women in this study were between the ages of 40 and 60 and did not have osteoporosis. The women were treated with alendronate sodium doses from 5 to 40 mg for six weeks and the dosages were well-tolerated. (PTX 116 at 1399).

Merck then sponsored a study investigating the effects of a range of different oral doses of alendronate for the treatment of osteoporosis. (PTX 69). The results of this study were published by Chestnut in 1995 in the *American Journal of Medicine*. The Chestnut study lasted for two years and involved 188 women with osteoporosis. (PTX 69; Yates at 502–504). Of these women, 31 were exposed to placebo, 32 to 5mg, 30 to 10 mg, 32 to 20 mg and 63 to 40 mg of alendronate sodium. (PTX 69 at Table 1). As of 1996, the Chestnut study was the only study that administered alendronate sodium to osteoporosis patients. (PTX 69; Markowitz at 478–479). Chestnut reported that nine women

6. Maconi, *The American Journal of Gastroenterology*, (1995) (PTX 90).

7. Harris, *Journal of Clinical Endocrinology and Metabolism*, (1993) (PTX 116).

discontinued alendronate sodium therapy due to gastrointestinal side effects that included nausea, dyspepsia, mild esophagitis/gastritis and abdominal pain. (PTX 69 at 150; Markowitz at 479–482; Fennerty at 265–66). Nine women withdrew from treatment because of these side effects: seven women withdrew from the 40 mg dose, one woman withdrew from the 20 mg dose and one woman withdrew from the group taking between 5 and 10 mg doses. (PTX 69 at 150; Markowitz at 479–482; Fennerty at 266; Yates at 539–540). Chestnut also reported that the gastrointestinal side effects “occurred primarily in the first year during treatment with 40 mg alendronate.” (PTX 69 at 150, col. 1). Dr. Fennerty testified that the fact that 11.1% (7 out of 63) withdrew from the 40 mg alendronate dose was noteworthy within the context of a clinical trial.⁸

Teva contends that the April and July 1996 editions of the *Lunar News* render claims 29 and 37 of the ’329 Patent obvious. The July 1996 *Lunar News* issue contained a section entitled, “Update Bisphosphonate.” (PTX 29 at 23). The section discusses bisphosphonates as a treatment for osteoporosis. *Id.* In reference to the use of alendronate for treatment of osteoporosis, it states that “[s]ome United States physicians are reluctant to treat because of: a) side effects; b) difficulty of dosing; and (c) high costs (\$700/year).” (PTX 19 at 23). To address the difficulty of dosing and high costs the article suggested:

The difficulties with oral bisphosphonates may favor their episodic (once/

week) or cyclical (one week each month) administration. Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

PTX 29 at 23. In a section entitled “Update: Bisphosphonates,” the April 1996 edition of the *Lunar News* discusses difficulties of the dosing regimen associated with alendronate and states:

one of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is bioavailable. Even coffee or juice reduces this by 60%, and a meal reduces it by > 85%. Alendronate must be taken, after an overnight fast, 30–60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly maintain chronically. An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested.

DTX 417 at 31. (citations omitted).

iii. *Differences Between the Prior Art and the Claims at Issue*

The Court concludes that the prior art cited above demonstrates that the suggestion to give 40 or 80 mg of alendronate sodium to treat or prevent osteoporosis was not clinically useful or obvious in July 1997 because of the known dose-related gastrointestinal side effects. Further, the

8. The Court concludes that studies dealing with Paget’s disease are not relevant to its analysis because it was well-known to those of ordinary skill in the art that patients with Paget’s disease tolerate higher doses of alendronate than patients with osteoporosis. (Papapoulos at 710–711; PTX 112 at 153; PTX 113 at 169; see also PTX 300 at 26). Thus,

the Court finds that tolerability of alendronate sodium from studies involving Paget’s patients should not be extrapolated to a discussion of osteoporosis about the tolerability of alendronate. For this reason, the Court will not address studies dealing with Paget’s disease and the tolerability of higher doses of alendronate sodium.

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Court is not persuaded that the two *Lunar News* articles, not published in peer-reviewed journals or authored by one skilled in the art, either alone or in combination, overcame the serious side effect concerns associated with higher dosage units of alendronate sodium. For example, Dr. Fennerty, whom the Court finds very credible, testified that in light of the prior art, any physician would have been “extraordinarily concerned” to suggest a 40 or 80 mg dose because alendronate sodium was a new compound that had been associated with dose-related injury and severe injuries in case reports. (Fennerty at 270–271; see also PTX 69, 91, PTX 300 at 14). In this regard Dr. Fennerty testified:

Q: Now in July of '97 or any period preceding that, what would your opinion be about a suggestion that you give 40 or 80 milligrams of alendronate to an osteoporotic woman?

A. Given what I just described, a new compound, a Dear [D]octor letter, publications in the New England Journal of severe caustic injury, smattering case reports around that, the Chestnut [sic] paper before talking about as you go up on a dose, that you may be seeing more adverse effects, the smattering of papers, and now animal data showing that types of patients that use NSAIDS use some higher dose of these compounds, shows evidence of gastric injury in the model, I would have been extraordinarily concerned about anybody suggesting that this was a useful clinical approach at that point and time.

(Fennerty at 270–271). Additionally, Dr. Papapoulos testified about the concerns of side effects associated with the suggestion in the July 1996 *Lunar News* where he stated, “[Lunar News] is using 40 and 80 not on any scientific rationale, but because it is available. Secondly, he doesn’t tell us how he’s going to address the issue

of side effects, which is one of the main points in this particular article.” Papapoulos at 665–666. Thus, in light of the case reports, and the Chestnut study, in conjunction with observations written about alendronate by Dr. Fleish, the Court concludes that the *Lunar News* references did not render the seven-fold daily dose of alendronate for the treatment and prevention of osteoporosis obvious given the clearly documented and known dose related gastrointestinal side effects associated with high doses (over 20 mg) of oral alendronate.

First, the April 1996 *Lunar News* did not deal with the specific dosages of 70 or 35 mg in relation to its discussion of once-weekly dosing of alendronate. Second, the July 1996 *Lunar News* listed 40 and 80 as compared to 70 and 35 mg dosages as suggested by the '329 Patent and did not deal with the problem of known gastrointestinal side effects. Additionally, in reaching its conclusion, the Court gives more weight to the prior art references written and reviewed by those skilled in the art such as the Chestnut study and the De Groen case report as opposed to the *Lunar News*, a quarterly newsletter written by someone without a Ph.D. or MD. in the applicable field.

iv. *Secondary Indicia of
Non-Obviousness*

As for the secondary considerations of non-obviousness, the Court finds that Merck has presented sufficient evidence to show that the 35 mg and 70 mg once-weekly dosing of Fosamax was commercially successful. On this issue, the Court finds Dr. Vellturo’s testimony persuasive. Dr. Vellturo testified regarding the evidence of increased sales after the launch of once-weekly Fosamax.

Originally, Merck’s Fosamax osteoporosis product line consisted of once-daily 10 and 5 mg Fosamax tablets. (D.I. 138 at

32). Dr. Vellturo testified that daily Fosamax was a successful product that enjoyed an average increase in sales of 152 million dollars per year for each of the four years preceding the introduction of the once-weekly Fosamax. (Vellturo at 718–720; PTX 166; PTX 300 at 37). In 2001, the first full year following the launch of the once-weekly dosing regimen, the sales increase was 343 million dollars, more than double the expected increase, without any corresponding relative increase in expenditures. (Vellturo at 719–720; PTX 166; PTX 300 at 37).

The Court finds that further evidence of the success of the once-weekly dosing regimen is present in the prescription data for the Fosamax tablets. A sharp increase in physician adoption of Fosamax upon the introduction of the once-weekly dosing regimen is manifested in the number of total prescriptions reported each month for Fosamax. (Vellturo at 723; PTX 164; PTX 300 at 32, 33, 36). The marked increase in prescription volume of once weekly dosages of Fosamax tablets is more compelling in light of its effects on the osteoporosis market in general. FAME is an acronym for the four prescription drug products whose primary indication is for the treatment of osteoporosis, (*i.e.*, Fosamax, Actonel, Miacalcin, and Evista). (Vellturo at 722, 753–754). IMS is a data collection firm specializing in data reflecting the prescribing patterns of physicians and in prescription volume data. (Vellturo at 716–717). Within six months of its launch, once-weekly Fosamax tablets became the most prescribed drug in the FAME market. (PTX 164; PTX 165; PTX 300 at 33). Based on the IMS data points present in the plot of monthly total prescriptions, it can be calculated that the Fosamax franchise share of the FAME market grew from 45 % to 55 % in the first six months after the introduction of the

once-weekly dosing regimen. (PTX 164; PTX 300 at 33).

Teva's expert Dr. Rozek testified that the increase in Fosamax sales could be due to other factors such as the increasing number of Americans over the age of sixty, the increasing awareness of osteoporosis, an increase in the number of people seeking treatment for osteoporosis and Merck's marketing efforts. However, the Court finds Dr. Rozek's explanation unpersuasive because he offered no affirmative opinion as to what affect these factors would have on the analysis of the FAME market as a whole or with Fosamax individually. (Rozek at 871–72; 869; 878). In fact, Dr. Rozek testified the he was “not instructed to do anything affirmative with regard to the measuring of any relationship that might exist between the [’329 Patent] and sales, or success of Fosamax.” (Rozek at 869). In the Court's view, Dr. Rozek's suggestion that there are factors that Dr. Vellturo should have considered, is not sufficient to rebut the affirmative evidence of the commercial success of the once-weekly dosing regimen. (Rozek at 878–79). Also, the Court concludes that Merck has shown a sufficient nexus between the claimed secondary considerations and the patented method given the testimony of Dr. Vellturo and the timing of the launch of the once-weekly dosing regimen for Fosamax. Accordingly, the Court has given the above discussed secondary considerations the importance they deserve in reaching its conclusion of nonobviousness. *See Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.* 976 F.2d 1559, 1573 (Fed.Cir.1992) (noting the importance of secondary considerations in the obviousness analysis).

v. Summary

In sum, the Court concludes that Teva has not proven by clear and convincing evidence that it was obvious to combine

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the *Lunar News* suggestions in light of the knowledge of one of ordinary skill in the art of the gastrointestinal side effects accompanying large doses of oral alendronate. In addition, the Court finds that the significant secondary considerations offered by Merck undermine any claim of obviousness, and accordingly, the Court concludes that Teva has not proven by clear and convincing evidence that the '329 Patent was obvious in light of prior art.

V. Unenforceability Due To Inequitable Conduct

A. The Inequitable Conduct Standard

[23–25] As a general matter, patent applicants and their patent attorneys have a duty of candor, good faith and honesty in their dealings with the PTO. 37 C.F.R. § 1.56(a). The duty of candor, good faith and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to the patent applicants or their attorneys which is material to the examination of the patent application. *Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed.Cir.1999). Breach of the duty of candor, good faith and honesty may constitute inequitable conduct. *Id.* If it is established that a patent applicant engaged in inequitable conduct before the PTO, the entire patent application so procured is rendered unenforceable. *Kingsdown Medical Consultants v. Hollister Incorporated*, 863 F.2d 867, 877 (Fed.Cir.1988).

[26, 27] A patent applicant engages in inequitable conduct before the PTO when he withholds or misrepresents information material to the patentability of his invention, with an intent to deceive. *See Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1064 (Fed.Cir.1998); (citing *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed.Cir.1995)). Inequita-

ble conduct encompasses affirmative misrepresentations of material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive. *Baxter Int'l, Inc. v. McGaw Inc.*, 149 F.3d 1321, 1327 (Fed.Cir.1998) (citing *Nobelpharma*, 141 F.3d at 1068–71). In order to establish unenforceability based on inequitable conduct, Teva must prove, by clear and convincing evidence, that material information was intentionally withheld for the purpose of misleading or deceiving the patent examiner. *See Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed.Cir.1995) (citation omitted).

[28] A determination of inequitable conduct entails a two step analysis. First, the court must determine whether the withheld information meets a threshold level of materiality. A reference is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. *See id.* This determination is not the end of the inquiry with respect to intent. The Federal Circuit has stated that, “materiality does not presume intent, which is a separate and essential component of inequitable conduct.” *See Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed.Cir.1990) (internal citation omitted).

[29] After determining if the applicant withheld information that is material, the court must then determine whether the evidence demonstrates a threshold level of intent to mislead the PTO. *See Baxter*, 149 F.3d at 1327. “Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent.” *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed.Cir.1996). Therefore, in order to satisfy the intent to deceive ele-

ment of inequitable conduct, the conduct when viewed in light of all of the evidence, including evidence of good faith, must demonstrate sufficient culpability to require a finding of intent to deceive. *See Paragon Podiatry Lab., Inc. v. KLM Lab, Inc.*, 984 F.2d 1182, 1189 (Fed.Cir.1993).

[30] The initial determinations of materiality and intent to deceive are questions of fact. *See Monon Corp. v. Stoughton Trailers, Inc.*, 239 F.3d 1253, 1261 (Fed.Cir.2001) (citation omitted). Once these facts are established, the court should then weigh the findings and their premises and determine, in its discretion, whether to hold the patent unenforceable. *See ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 547 (Fed.Cir.1998).

B. Whether Dr. Yates Engaged In Inequitable Conduct Before the PTO Rendering The '329 Patent Unenforceable

[31] Teva contends that Dr. Yates engaged in inequitable conduct before the PTO rendering the '329 Patent unenforceable. Specifically, Teva contends that Dr. Yates intentionally withheld the July 1996 edition of the *Lunar News* from the Patent Examiner.

In response, Merck contends that the July 1996 *Lunar News* was not considered material because it was cumulative to the cited prior art. Merck further contends that Dr. Yates did not make any material misrepresentations to the PTO, and that Teva cannot establish an intent to deceive the PTO by clear and convincing evidence.

1. The Allegedly Withheld Prior Art

In the Court's view, the July 1996 *Lunar News* has some degree of materiality because it has relevance to the claimed invention, specifically, the recommended once-weekly dosage level of alendronate for osteoporosis patients. Additionally,

the Court finds that it is not cumulative to the cited prior art, specifically the April 1997 *Lunar News* because, although the April edition mentions a 40 mg dose of alendronate it does not suggest a 40 or 80 mg dose in the context of once-weekly dosing as the July 1996 edition of the *Lunar News* does. However, as previously discussed, the Court finds that the July 1996 *Lunar News* does not reflect the claimed invention directly and does not render the claimed invention invalid as either obvious or anticipated. *See, e.g., Life Technologies, Inc. v. Clontech Labs. Inc.*, 224 F.3d 1320, 1325 (Fed.Cir.2000) (citing 35 U.S.C. § 103(a) and stating that "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute").

2. Intent to Deceive

The Court concludes that Teva has failed to meet its burden of demonstrating a prima facie showing of intent to deceive the PTO. As to this issue, Teva contends that Dr. Yates' testimony indicating that he did not read the July 1996 *Lunar News* was not credible in light of the fact that in September 1996, Dr. Yates received a memorandum discussing *Lunar News'* comments about alendronate, with the relevant portions of the July issue attached. Further, Teva argues that Dr. Yates' testimony that he did not focus on the July 1996 issue again on May 21, 1997 at a meeting with Lunar Corp., where the July 1997 issue was attached as an agenda item, is not credible.

The Court finds that this evidence of intent to deceive falls short of the applicable standard. Dr. Yates testified unequivocally that he had never seen the statements regarding once-weekly dosing of alendronate in the July 1996 *Lunar News* prior to this litigation. (Yates at 533-34; 572-573; 575). Additionally, in

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reference to the September 1996 memo that was circulated with the July 1996 *Lunar News* as an attachment, the Court recognizes that there were twelve pages attached to the original memo and the relevant article in the July 1996 *Lunar News* was the last page. Based on this, the Court finds Dr. Yates' testimony that he did not read the July 1996 *Lunar News* article in September 1996, credible. Likewise, the Court does not find Teva's assertion that Dr. Yates should have read the article that was attached to the agenda at the May 1997 meeting, probative of Dr. Yates' intent to deceive because attendees, including Dr. Mazess, did not recall whether the once-weekly dosing concept was specifically addressed at the meeting. (Mazess Dep. at 180:19-181:7; Beckman Dep. at 131:1-23; Magri Dep. at 105:7-25; Sherwood Dep. at 146:17-23, 147:11-148:3). Further, the Court finds that even if once-weekly dosing was discussed at the meeting, the focus of the discussion was more likely than not centered on the April 1997 edition of the *Lunar News*, which was disclosed to the examiner, rather than the July 1996 edition because the April 1997 edition came out in the month preceding the meeting.

[32] "In a case involving an omission of a material reference to the PTO, there must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known reference." *Baxter Int'l, Inc. v. McGraw, Inc.*, 149 F.3d 1321, 1329 (Fed.Cir.1998). The Court concludes that Teva has proffered insufficient evidence of an intent to deceive on the part of Dr. Yates. Accordingly, the Court cannot conclude that Dr. Yates engaged in inequitable conduct before the PTO by failing to disclose material prior art.

Conclusion

For the reasons discussed, the Court concludes that Teva has not proven that

the patent-in-suit is invalid or that Merck engaged in inequitable conduct before the PTO.

An appropriate Order will be entered.

ORDER

NOW THEREFORE, For The Reasons discussed in the Opinion issued this date, IT IS HEREBY ORDERED this 28th day of August 2003 that:

1) Defendant's Motion to Preclude Plaintiff Merck from Relitigating the Factual Findings Underlying the Decision in *Teva Pharmaceuticals Ltd. et al. Instituto Gentili Spa et al.* (D.I.113) is **DE-NIED**.

2) Plaintiff shall submit a Proposed Order within ten (10) days of its receipt of this Memorandum Opinion. Defendant may stipulate to Plaintiff's Proposed Order, or file any objections within ten (10) days of their receipt of the Proposed Order.



Randall TESTERMAN, Plaintiff,

v.

The INTERNATIONAL UNION, Automobile, Aerospace and Agricultural Implement Workers of America (UAW); and Local Union 1183, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW), Defendants.

No. CIV.A.98-620-KAJ.

United States District Court,
D. Delaware.

Sept. 23, 2003.

Employee sued union, challenging union's withdrawal of appeal of employee's

EXHIBIT G

No. 04-1005

IN THE
United States Court of Appeals
FOR THE FEDERAL CIRCUIT

MERCK & CO., INC.,

Plaintiff-Appellee,

—v.—

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE IN CIVIL ACTION NO. 01-CV-0048,
JUDGE JOSEPH J. FARNAN, JR.

**BRIEF FOR DEFENDANT-APPELLANT
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**CERTIFICATE OF INTEREST FOR
TEVA PHARMACEUTICALS USA, INC.**

Counsel for defendant-appellant Teva Pharmaceuticals USA, Inc.,
certifies the following:

1. The full name of every party represented by me is:

Teva Pharmaceuticals USA, Inc.

2. The names of the real parties in interest represented by me are:

See response to number 1.

3. All parent corporations and any publicly held companies that
own 10 percent or more of the stock of the party represented by me are:

Teva Pharmaceuticals Europe B.V.
Teva Pharmaceuticals Industries, Ltd.

4. The names of all law firms and the partners or associates that appeared for the parties represented by me in the trial court or are expected to appear in this Court are:

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STATEMENT OF RELATED CASES

No other appeal in or from this action was previously before this or any other appellate court. Counsel for appellant is not aware of any case pending before this Court that will be directly or indirectly affected by the outcome of this appeal.

STATEMENT OF JURISDICTION

The district court's jurisdiction was based on 28 U.S.C. § 1338(a) because the complaint arose under the patent laws. This Court has jurisdiction over the appeal under 28 U.S.C. § 1295(a)(1). The district court entered judgment September 24, 2003, and Teva filed a timely notice of appeal September 25, 2003.

STATEMENT OF ISSUES

1. Whether the district court erred in failing to construe “about” in claims 23 and 27 of U.S. Patent 5,994,329 patent accordance with its ordinary meaning of “approximately,” thereby rendering the term redundant.
2. Whether the district court erred in finding, based solely on its erroneous claim construction, that a prior art reference did not anticipate the claimed invention.
3. Whether the district court, having found that the claimed invention was “known,” erred in failing to find that the subject matter would have been obvious to a person of ordinary skill in the art.

INTRODUCTION

The patent in suit, U.S. Patent 5,994,329, claims methods of treating and preventing osteoporosis by administering alendronate sodium once per week, at a dosage strength seven times the known daily dose. Both this drug and its utility for osteoporosis under a daily dosing regimen were well known before Merck filed its application for the '329 patent. Moreover, as the district court found, the prior art taught that the drug could be administered once per week at a larger dose, and as Merck conceded, persons skilled in the art would have recognized that the appropriate weekly dose would be seven times the daily dose. In fact, a publication widely distributed to clinicians, the *Lunar News*, actually proposed such a dosing regimen long before Merck's invention date.

However, instead of finding the claims to weekly administration invalid as anticipated or obvious — the latter a result reached by the British High Court of Justice with respect to the European counterpart of the patent in suit — the district court rejected Teva's validity challenge. It did so for reasons that reflect a misunderstanding as to what constitutes a patentable invention.

The district court based its decision primarily on a finding that doctors treating osteoporosis patients, despite the admitted recognition of the

efficacy of the once weekly dosing regimen, would have refrained from prescribing that regimen because of fears that certain side effects would occur more frequently with the administration of higher doses of alendronate. The patent's claims, however, say nothing about the comparative safety of the weekly dosing regimen. All that Merck claimed — the weekly dosing regimen itself — was disclosed in its entirety in the prior art, in particular the *Lunar News*, and that publication therefore anticipated the claims and rendered them obvious. Moreover, to the extent the claimed method turned out to be free from side effects, then the same method described in the prior art must be free from side effects as well. A valid patent cannot be granted merely for observing the result of a method that is already disclosed in the prior art.

The district court rejected these invalidity arguments only through a combination of incoherent claim construction and an irrelevant (and unsupported) finding that persons of ordinary skill in the art would not have taken the *Lunar News* seriously. The judgment based on these rulings must be reversed.

STATEMENT OF THE CASE

In October 2000, Teva filed an amendment to an existing Abbreviated New Drug Application directed to alendronate. The amendment sought approval to market generic versions of Merck's 70 mg alendronate tablets for once-weekly dosing for treatment of osteoporosis. Because Merck had listed several patents in connection with those tablets in the "Orange Book," Teva certified that it believed that the commercial marketing of its proposed generic product would not infringe the patents or that they were invalid or unenforceable. Merck filed suit within the requisite 45 days. Two other suits followed shortly thereafter, one involving a newly issued patent and the other involving the same set of patents but a different dosage strength — 35 mg for dosing once per week for the prevention of osteoporosis.

All three suits were consolidated, and before trial, Merck dropped all claims except infringement of claims 23 and 37 of the '329 patent and claim 1 of U.S. Patent 4,621,077. With respect to the '077 patent, the parties agreed to be bound by this Court's decision on the then-pending appeal of the district court's judgment with respect to it. (A7, A92-94).¹ Thus, the

¹ On October 30, 2003, this Court, in a 2-1 decision, found that that Teva's ANDA filing infringed the '077 patent, and that the patent term extension for that patent is valid. Teva has petitioned for rehearing or rehearing en banc, and that petition is pending.

only issues for trial were the validity and enforceability of claims 23 and 37 of the '329 patent.

Before the trial, the parties litigated the validity of the corresponding patent in the United Kingdom, employing for the most part the same witnesses who were later to testify in the United States. On January 22, 2003, the British High Court of Justice entered judgment that the claim of the corresponding European Patent was invalid on alternative grounds, one of which was that the claimed invention would have been obvious. In doing so, it made factual findings, many of which addressed the very issues that were later disputed in the trial of this case. (A3027-34). In October 2003 the British Court of Appeal affirmed the judgment of the High Court, although it did not reach the obviousness question. Following the decision of the High Court, Teva moved to preclude Merck from re-litigating certain factual findings that informed that court's decision. The district court, however, denied the motion after trial.² (A23).

² The court held that those findings were "mixed questions" of law and fact, and were therefore not susceptible to collateral estoppel in light of the differences between the legal standards in the United Kingdom and the U.S. The district court also held that the High Court's decision was based on "alternative" grounds, and that the findings relating to obviousness were therefore not essential to that court's judgment. (A21-23).

The district court conducted a four-day trial in November 2002, and issued its opinion August 28, 2003. The district court found that Teva had failed to prove that the July 1996 issue of *Lunar News* anticipated claims 23 and 37 of the '329 patent. It based its holding on its construction of the word "about," which appears in the same context in both claims. Rejecting the term's ordinary meaning of "approximately," the court held that the inventors had coined a special meaning for the term, and that the *Lunar News* did not anticipate the claims under that special meaning.

Notwithstanding its finding that the effectiveness of a once-weekly dosing regimen of alendronate was "known," the district court held that the claimed invention of that same regimen would not have been obvious to a person skilled in the art. In doing so, the court never identified a single significant difference between the dosing regimen taught by *Lunar News* and the claimed invention. In fact, it found that the *Lunar News* suggested once-weekly administration of alendronate (A66), but then did not consider whether the invention would have been obvious in light of the minor differences it found between the claims and that prior art.

Despite Merck's acknowledgement that the *Lunar News* articles taught a safe and effective weekly dosing regimen, and that a person of ordinary skill would have recognized both that effectiveness and that the

appropriate dose should be seven times the daily dose, the district court rejected the articles because, in its view, persons of ordinary skill would have been reluctant to follow their teachings.³ Thus, the district court in effect held that a prior art disclosure that is in fact scientifically sound and that teaches a later-claimed invention can be nullified if persons skilled in the art would have been skeptical of it at the time it was published.

STATEMENT OF FACTS

I. MERCK'S DAILY DOSE ALENDRONATE

In September 1995, Merck introduced “Fosamax” for the treatment of osteoporosis and Paget’s disease of bone, two diseases characterized by excessive bone “resorption.” Merck recommended a daily dose of one 10 mg tablet for treatment of osteoporosis and a daily dose of one 40 mg tablet for treatment of Paget’s disease. (A2843). In 1996, Merck introduced a 5 mg daily dose tablet for prevention of osteoporosis.

The active ingredient of Fosamax is alendronate monosodium salt trihydrate (“alendronate sodium” or “alendronate”), which is a salt prepared

³ The British High Court characterized this argument as the “fear defense,” and rejected it, finding as a fact that persons skilled in the art would not have been skeptical of or alarmed by the prospect of once-weekly dosing at a higher dose. (A3032-34).

from alendronic acid. The dosage strengths in the Fosamax tablets were all specified on an alendronic acid active basis, that is, the amount of the salt in the tablet was sufficient to yield the same number of molecules of the active chemical entity as 5 mg, 10 mg and 40 mg of alendronic acid. Thus, Merck's "10 mg" dose actually contained 13.05 mg of the alendronate sodium salt, because that much salt was necessary to deliver the same amount of therapeutically active substance to the bone as 10 mg of alendronic acid. (A2841, A2845).

Merck had recognized early in the development of the drug that if not administered properly, it could cause irritation and even damage to the esophagus. To avoid these effects, Merck therefore specified complicated and inconvenient dosing instructions. Patients were required to take the drug before eating, and to take it with a large glass of water to help ensure that the tablet would quickly pass through the esophagus to the stomach. They then had to remain upright for half an hour, and could not eat during that period. (A220-22). These dosing instructions were universally recognized as burdensome and as deterrent to patients' ability and willingness to take the drug. (A222).

Merck's clinical trials demonstrated that for patients who followed these instructions, the incidence of adverse gastrointestinal side effects was

no greater than that for patients who were administered a placebo. Articles published by Merck authors about those trials showed that the 5 mg, 10 mg and 20 mg daily doses were “well tolerated.” (A254-55; A259-63; A655; A2318-24 at 2322; A3000-11 at 3007; A2409-16 at 2413). At a 40 mg daily dose, one clinical trial showed that 90 percent of osteoporosis patients tolerated the drug (A1102-10 at 1108), and in trials of the drug on patients with Paget’s disease, the drug was “well tolerated,” with side effects indistinguishable from those of placebo, even at a dose of 80 mg every day. (A269; A272-75; A1115; A2297; A2423). Based on Merck’s clinical trials, the FDA approved Fosamax for the treatment (10 mg daily) and prevention (5 mg daily) of osteoporosis and for the treatment of Paget’s disease (40 mg daily).

Actual clinical experience, however, yielded occasional reports of severe cases of esophageal erosion. Merck’s principal inventor described such cases as “rare.” (A652; A658-59). Clinical case reports established that these effects were caused by sustained and repetitive exposure of the esophagus to the drug. (A3836). Merck investigated and decided that the vast majority of these isolated cases were attributable to patients’ failure to follow Merck’s dosing instructions – to take with pill with a large glass of water and to remain erect for half an hour. (A4818-19). This failure

resulted in “pill esophagitis,” i.e., the pill became lodged in the patient’s esophagus for a period, causing irritation. (A377-78; A536-38; A1046-54; A2364-65; A4817-20). Merck’s response to these cases was to reinforce its dosing instructions by sending a “Dear Doctor” letter to physicians urging them to instruct their patients carefully. (A377; A1289-90). This remedy was effective, and the incidence of severe side effects dropped essentially to zero by the time the ’329 patent was filed for in July 1997. (A378-79; A663-64; A3191).

II. WEEKLY ADMINISTRATION OF ALENDRONATE WAS KNOWN TO PERSONS SKILLED IN THE ART

A. Persons Skilled in the Art Knew that Alendronate Could be Administered Less Frequently than Every Day

Alendronate, like other bisphosphonates, is absorbed into bone tissue. Cells responsible for bone resorption, called osteoclasts, take up alendronate from the bone surface. Alendronate is toxic to those cells, so that their function – resorbing bone – is inhibited. Based on published reports of preclinical research with alendronate, it was well understood before 1997 that alendronate would inhibit bone resorption effectively even if it were administered less frequently than once per day. (A238-39; A643-44; A1348-55 at 1353; A1357-66 at 1358; A1367-76 at 1369; A2958-65 at 2958; A2975-80 at 2976; A2981-87 at 2982; A2988-98 at 2990). It was also

well understood that the absorption of alendronate was linear with dose up to 80 mg. (A241-42; A1029-32 at 1031). For these reasons, Merck conceded and the district court found that persons skilled in the art would have recognized that alendronate would be effective if administered once per week, and Merck conceded that they would have recognized that such a weekly dose should be about seven times the daily dose. (A59; A238-39; A643-44; A776-78).

B. The *Lunar News* Taught Once-Weekly Administration of Alendronate for Osteoporosis

Not only did persons skilled in the art understand that alendronate could be effectively administered once per week at a multiple of the daily dose to obtain the same therapy as daily treatment, the prior art specifically disclosed and recommended that regimen for the treatment and prevention of osteoporosis. A widely read publication called the *Lunar News* taught that concept long before Merck's invention.

Osteoporosis is often diagnosed by using a device called a "bone densitometer." Dr. Richard Mazess, a Professor Emeritus at the University of Wisconsin, developed the bone densitometer, and established the Lunar Corporation to make and market the devices. Dr. Mazess's education included a Ph.D. in physical anthropology, and he had conducted research in physiology, medical physics and bone disease, had published widely in the

bone disease field, had acted as a principal clinical investigator for clinical trials related to bone disease, and was a recognized authority in his area of expertise. (A225-26; A4822-35).

Under Dr. Mazess's direction, the Lunar Corporation published a newsletter called *Lunar News*, which it distributed to physicians and others involved in the treatment of bone disease. The *Lunar News* included review articles on various topics related to bone disease. (A223-27). It provided exhaustive reviews of current medical literature, and the bibliographies in each issue included hundreds of articles. (A227; *see also*, A3036-79 at 3069-79; A3080-15 at 3106-15). The *Lunar News* was widely read; each issue was distributed to 15,000 to 20,000 physicians. (A4836). Both parties' principal testifying experts received it and found it useful because it provided valuable distillations of the pertinent literature. (A226-27; A756-57; A781). It was circulated within Merck, and Merck's expert and its inventors regarded it as a valuable resource. (A781; A4865-66).

In April 1996, only seven months after Merck introduced Fosamax in tablet form for once-daily administration and more than a year before Merck filed the '329 patent application, Dr. Mazess disclosed to the bone disease community the specific concept of dosing alendronate once weekly at about seven times the daily dose. The April 1996 *Lunar News* included an article

entitled “Update: Bisphosphonates.” The article first focused on the difficulties associated with taking alendronate tablets:

One of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is available. Even coffee or juice reduces this by >60%, and a meal reduces it by >85%. Alendronate must be taken, after an overnight fast, 30-60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly to maintain chronically.

(A3066). Merck’s expert conceded that these statements were correct.

(A772-74). The article went on to suggest two dosing regimens as solutions to the problems it had identified:

An *intermittent* treatment program (for example, *once per week*, or one week every three months) needs to be tested.

(A3066; emphasis added). The article concludes with citations to 14 references from the medical literature, including the Chesnut article, the primary reference on which the district court relied to reject the *Lunar News*. (A3066, ref. 4).

It is undisputed that the reference to “needs to be tested” would have been understood to mean subjected to a clinical trial for the purpose of obtaining regulatory approval, as distinguished from tried as a speculative experiment. (A244-46). Although the article does not specify a dosage strength for the weekly dose, Merck’s expert conceded and Merck has never

disputed that a person skilled in the art would have recognized that the weekly dose for the “once per week” dosing regimen should be seven times the daily dose. (A243-44; A246-47; A776-78; *see also*, A643-44).

Thus, as of April 1996, the *Lunar News*, together with the knowledge in the art, taught the concept of the claimed invention: administer alendronate once-weekly at seven times the daily dose. In addition, it taught the rationale for that concept that Merck included in its patent application more than a year later: patient convenience and compliance with dosing instructions. Finally, it provided the references on which the author had consulted, several of which are also discussed in the '329 patent.

In July 1996, the next issue of *Lunar News* reiterated the suggestion of once-weekly dosing of alendronate. First, the article, again called “Update: Bisphosphonate,” referred to the dosing difficulties associated with alendronate:

Bisphosphonates are a major focus for researchers dealing with osteoporosis. . . . Some U.S. physicians are reluctant to treat because of: (a) side effects, (b) difficulty of dosing, and (c) high costs (\$700/year). First, Merck recently sent a letter to physicians warning of esophagitis. Some physicians report that 5 to 15% of patients experience gastric and/or esophageal distress, but most have seen no side effects. Serious side effects of ulceration and stricture appear rare. Second, some patients also stop alendronate because of the dosing difficulty. The limited bioavailability of alendronate (0.8%) requires that it be taken on an empty stomach upon awakening with a full glass of water (not tea, coffee, or juice),

and the patient must remain upright for 30 to 60 minutes. A few elderly women can tolerate this regime for only a week or two. Third, some U.S. patients, whose insurance does not cover drug costs, are finding alendronate expensive. . . .

The article then suggests a solution to these problems:

The difficulties with oral bisphosphonates may favor their episodic (*once/week*), or cyclical (one week each month) administration. *Even oral alendronate could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.*

(A3102; emphasis added). The article ends with citations to 16 recent scientific publications relating to the use of bisphosphonates.

The July 1996 *Lunar News* accurately describes the dosing problems associated with alendronate, including the reports of severe esophageal injury, which it accurately characterizes as “rare.” (A652; A658-59). It then suggests solutions, one of which is to administer alendronate once per week at a higher dose. Dr. Mazess provided an advantage for doing so – to “avoid dosing problems” – that is the principal advantage Merck touted in its patent application filed a year later.

The weekly doses Dr. Mazess suggested, 80 mg and 40 mg, differed only slightly from exactly seven times the daily doses. The reason for his choice of dose was that 40 mg tablets were available in the marketplace – Merck was selling them as a daily dose for the treatment of Paget’s disease. (A235-36; A765-66; A2841). Exact multiples of the daily dose – 35 mg and

70 mg tablets – were not then commercially available. Dr. Mazess was thus suggesting that the then available tablets could be administered for once/weekly doses, and would have the same therapeutic effect as the lower doses administered daily. Although the district court did not find the patent claims invalid in light of the *Lunar News*, it found that the July issue was more material than any prior art references that the patent examiner considered. (A75).

III. THE '329 PATENT

Merck filed for the '329 patent July 22, 1997, and the patent issued November 30, 1999. The patent discloses and claims a dosing regimen for alendronate to treat or prevent osteoporosis. The patent claims a method of “treatment” of osteoporosis by administering “about 70 mg” alendronate sodium trihydrate on an “alendronic acid active basis” once per week (claim 23) and a method of “prevention” of osteoporosis by administering “about 35 mg” alendronate sodium trihydrate on an “alendronic acid active basis” once per week (claim 37). Specifically, the parties’ agreed text for claims 23 and 37, cast in independent form⁴, is:

23. A method for treating osteoporosis in a human comprising orally administering about 70 mg of alendronate monosodium trihydrate, on an alendronic

⁴ Claims 23 and 37 depend from several other claims.

acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

37. A method for preventing osteoporosis in a human comprising orally administering about 35 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

The idea behind the asserted claims is simple: instead of taking 10 mg or 5 mg of alendronate every day to treat or prevent osteoporosis, take seven times that amount once per week. The only difference between the claimed regimen and the prior regimen is the frequency of administration and the strength of the dose.

Although the asserted claims relate to the management of osteoporosis in humans, the '329 patent includes no data derived from the administration of alendronate to humans, and no data or examples demonstrating the efficacy of the claimed methods at treating or preventing osteoporosis in any species. (A218-19; A642-43). The absence of such data reflects the expectation among persons skilled in the art that the regimen would be effective, and Merck concedes that such persons would have recognized that those weekly doses recited the appropriate strengths. (A59; A238-39; A643-44; A776-78). Instead of clinical data, the patent specification refers to several articles from scientific journals to support its claims, most of which

were cited in the *Lunar News* a year earlier to support the author's recommendation of once-weekly administration. (See A3066; A3102).

The '329 patent specification recognizes that the inconvenience of the alendronate dosing regimen provides a motivation to administer the drug less frequently, and proposes the invention as a solution to that problem:

[B]ecause bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

(A999-1019, col. 2, line 67-col. 3, line 6);

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing.

(*Id.*, col. 4, lines 14-19).

A comparison of the *Lunar News* and the claimed invention demonstrates that Merck has patented the same concept for solving the same problems that Dr. Mazess had taught physicians treating bone disease a year earlier. Neither the district court nor Merck ever identified any contribution that Merck's inventors made over and above the disclosure of the *Lunar News*. In fact, the *only* difference the district court found between the two

was its erroneous conclusion that “80 mg” in the *Lunar News* is not “about 70 mg” in claim 23 and that “40 mg” is not “about 35 mg” in claim 37.

Notwithstanding that the *Lunar News* disclosures were *completely accurate and scientifically sound*, the district court discounted them because it found that persons skilled in the art would have been skeptical of Dr. Mazess’s insights, and been reluctant to employ the higher dose he advocated in light of alleged safety concerns. (A67-68). The district court thus adopted the “fear defense” that Merck had concocted for this litigation, which the British High Court had previously rejected. (A3032-34). The court, however, never explained the relevance of the “fear defense” to the validity of the patent claims, even if there were in fact a sound basis for it. In addition, it ignored that the evidence on which it relied to support the alleged apprehensions about side effects was the very information Merck had previously cited to the FDA to support the safety, i.e., the likely absence of side effects, for its then-proposed but untested 70 mg weekly dose.

SUMMARY OF THE ARGUMENT

The word “about” appears in both asserted claims to modify the amount of alendronate sodium in the weekly dose. The district court ignored the ordinary meaning of that word: “approximately.” The court instead

employed a meaning that not only is not supported by the patent itself, but makes the term redundant. There is no dispute that the *Lunar News*'s disclosure of weekly doses of 80 mg and 40 mg are "approximately" the same as the claimed doses of 70 mg and 35 mg. Under a correct construction of the term "about," July 1996 *Lunar News* anticipates both claims.

Even assuming the correctness of the court's construction, the claimed invention would have been obvious. The court found that weekly dosing of alendronate was "known," and the appropriate doses would have been apparent to those skilled in the art. The district court's rationale for discarding the prior art is legally irrelevant. Even accepting the district court's fact finding, the claims are invalid because the claimed invention would have been obvious.

ARGUMENT

I. THE STANDARD OF REVIEW

This Court reviews the district court's construction of "about 70 mg" and "about 35 mg," which appear in claims 23 and 37, respectively, *de novo*. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 969, 34 USPQ2d 1321, 1329 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). With respect to

anticipation, the Court reviews the district court's factual findings under the "clearly erroneous" standard of Fed. R. Civ. P. 52(a). However, whether the district court applied the correct legal analysis in addressing anticipation is a question of law. *See Apple Computer Inc. v. Articulate Sys., Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061-62 (Fed. Cir. 2000).

Obviousness is a question of law, and the ultimate determination of obviousness is reviewed without deference to the holding of the district court. *Brown and Williamson Tobacco Corp. v. Phillip Morris, Inc.*, 229 F.3d 1120, 1124, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). The obviousness determination is based on underlying factual inquiries, including 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ2d 459, 467 (1966). These factual determinations are reviewed for clear error. *Sibia Neurosciences, Inc. v. Cadus Pharmaceutical Corporation*, 225 F.3d 1349, 1355, 55 USPQ2d 1927, 1930-31 (Fed. Cir. 2000).

Finally, although Teva bears the burden of proof by clear and convincing evidence, that burden is more easily overcome where, as here, the most pertinent prior art (the April 1996 and July 1996 *Lunar News*) was

not before the patent examiner. *Sibia Neurosciences, id.* at 1355, 55

USPQ2d at 1931; *B.F. Goodrich Co. v. Aircraft Braking Systems Corp.*, 72

F.3d 1577, 1581, 37 USPQ2d 1314, 1316 (Fed. Cir. 1996).

II. THE DISTRICT COURT ERRED IN HOLDING THAT THE JULY 1996 *LUNAR NEWS* DID NOT ANTICIPATE THE CLAIMED INVENTION

A. The District Court Failed To Construe “About” in Claims 23 and 37 Correctly

1. The Ordinary Meaning of “About” is “Approximately”

The sole basis for the district court’s finding that the July 1996 *Lunar News* did not anticipate the claimed invention was its construction of claims 23 and 37. Those claims require the administration of “about 70 mg” and “about 35 mg,” respectively, of alendronate monosodium salt trihydrate “on an alendronic acid active basis.”

The meaning of the second of these terms, “on an alendronic acid active basis,” is undisputed. It defines the amount of alendronate monosodium salt trihydrate that provides the same amount of active substance as the recited amount of alendronic acid. Expressing the amount of drug “on an alendronic acid active basis” or “on an alendronic acid basis” provides a common denominator by which the various salts and hydrates of alendronic acid, which have different molecular weights, can be compared.

(A496-97). Thus, the dosage strength of Merck's weekly "70 mg" alendronate tablet is expressed on an alendronic acid basis, and the tablet actually contains more than 90 mg of alendronate monosodium salt trihydrate, because that much is required to provide the same number of active molecules as 70 mg of alendronic acid. (A2845). The use of such a common denominator is typical of pharmaceutical practice. (A497).

The district court recognized that the claim construction dispute concerned the meaning of "about" in the context of the claims. (A26-27). The first step in construing a term in a patent claim is to determine its "ordinary meaning"; a "heavy presumption" favors that ordinary meaning. *Texas Digital Systems v. Telgenix Inc.*, 308 F.3d 1193, 1202, 64 USPQ2d 1812, 1817 (Fed. Cir. 2002); *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331, 59 USPQ2d 1401, 1406 (Fed. Cir. 2001); *CCS Fitness v. Brunswick Corp.*, 288 F.3d 1359, 1366, 62 USPQ2d 1658, 1662 (Fed. Cir. 2002). "If the claim language is clear on its face, then [the court's] consideration of the rest of the intrinsic evidence is restricted to determining if a deviation from the clear language of the claims is specified." *Interactive*, 256 F.3d at 1331, 59 USPQ2d at 1407. The term

“about” has an ordinary meaning: “approximately.” (A27).⁵ Neither Merck nor the district court suggested a different ordinary meaning.

2. The Specification Supports the Ordinary Meaning

The district court ruled that in claims 23 and 47 “about” should not be accorded its ordinary meaning. Instead, it ruled that the specification had provided an alternative definition. According to the district court, “about 70 mg” means

the equivalent of 70 . . . mg of alendronic acid. . . . Simply put, no matter what the final weight of the actual active ingredient in the tablet is, it contains the same number of core molecules as 70 . . . mg of alendronic acid.

(A28). That is, according to the district court, “about 70 mg” does not mean “approximately 70 mg,” but instead means exactly 70 mg on an alendronic acid active basis.

In rejecting the notion that “about” means what it says, the district court relied on a passage from the specification that states:

Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated

⁵ Webster’s New International Dictionary (1993) (A5138-40); American Heritage Dictionary of the English Language (1978). (A5141-43).

otherwise herein. For example, the phrase “about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis” means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

(A999-1019, col. 11, line 65- col. 12, line 8; *see* A28-29). This passage is simply an explanation of why the different compounds, “alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof,” are specified on the basis of a common denominator – the amount of each required to yield the same amount of active ingredient as 70 mg of alendronic acid. (A402). According to the district court, however, the passage redefines “about” so that it no longer has its ordinary meaning. (A28-29). The district court’s based its conclusion on the following testimony, two questions from Merck’s counsel and answers from Teva’s expert witness, Dr. Russell, referring to that passage:

Q: I understand, but it is what it says, and perhaps the person wanted to say if it’s a certain salt one, you might use 71, and if it’s a certain salt 2, you might use 73. Isn’t that what’s indicated by this?

A: Possibly.

Q: But that’s what the definition says; right?

A: That is the definition as it’s described in the patent.

(A435-36). According to the district court, its interpretation of the witness's answer to these garbled questions trumps the ordinary meaning of "about."

(A32). In fact, the passage to which the testimony refers explicitly states that the dose should be reported on an alendronic acid active basis to account for the possible differences in molecular weights among salts. Indeed, Dr. Russell made his opinion clear:

Q. They're defining what is meant by acid active weight basis, but they're not defining what is meant by "about"; is that right?

A: Yes.

(A499). None of Merck's witnesses supported the district court's construction of "about 70 mg," and the district court never articulated how this passage represents a "clear" rejection of the ordinary meaning.

In reaching its conclusion, the district court ignored the specification's repeated use of both terms to refer to the same dosage strength. If "about" had the meaning the district court gave it, then there would be no need to use both "about" and "on an alendronic acid active basis" to describe the same dosage strength, because the former term would be redundant. Yet the specification repeatedly and uniformly employs both terms in quantifying the same dosage strength. First, in describing appropriate dosing ranges, the specification states:

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from *about* 8.75 mg to *about* 140 mg of the alendronate compound, *on an alendronic acid active weight basis*. . . .

(A999-1019, col. 12, lines 50-55). The patent then describes more specific ranges, each time defining them as, e.g., “*about* [a specific amount], *on an alendronic acid active weight basis*.” (Col. 12, line 56 – col. 13, line 7; emphasis added).

In the examples, the patent likewise repeatedly characterizes the same dosage strength using both “about” and “on an alendronic acid active basis,” e.g.:

Alendronate tablets or liquid formulations containing *about* 70 mg of alendronate, *on an alendronic acid active basis*, are prepared. . .

(Col. 17, lines 24 – 27 (emphasis added); *see also* col. 17, line 51 – col. 19, line 63).

On at least 15 different occasions the specification employs both terms (“about” and “on an alendronic acid basis”) in the same phrase to describe the same dosage strength. This consistent practice demonstrates that the patent drafters were not employing “about” as a synonym for “on an alendronic acid active basis.” Thus, “about” and “on an alendronic acid active basis” must mean different things. It is

undisputed that “on an alendronic acid active basis” defines the common denominator by which to compare dosage strengths of different salts of alendronic acid. “About,” therefore, must have its ordinary meaning of “approximately.”

The district court relied on Examples 7 and 8 to support its construction. (A29-30). However, those examples, like the others, employ both “about” and “on an alendronic acid active basis” to define the quantity of alendronate sodium. Thus, these terms cannot sensibly mean the same thing, and the district court’s holding that the specification defines “about” contrary to its ordinary meaning is in error.

3. The District Court’s Construction of “About” Makes the Term Superfluous in the Claims Themselves

The district court’s construction of “about” is also flawed because it renders superfluous the very word it construes. Thus, claim 23, rewritten to substitute the district court’s synonym for “about,” would read:

A method for treating osteoporosis in a human comprising administering, *on an alendronic acid active basis*, 70 mg of alendronate monosodium trihydrate, *on an alendronic acid active basis*, as a unit dosage according to a continuous schedule having a dosing interval of once weekly.

This absurd result cannot be correct. This Court has repeatedly held that a claim construction that makes a limitation superfluous must be rejected.

Elektro Instrument S.A. v. O.U.R. Scientific Int’l Inc., 214 F.3d 1302, 1307,

54 USPQ2d 1910, 1913 (Fed. Cir. 2000); *General American Transportation Corp.*, 93 F.3d 766, 39 USPQ2d 1801, 1803 (Fed. Cir. 1996). On the other hand, a construction in which “about” is accorded its ordinary meaning of “approximately” makes perfect sense and contains no superfluous limitations:

A method for treating osteoporosis in a human comprising administering *approximately* 70 mg of alendronate monosodium trihydrate, *on an alendronic acid active basis*, as a unit dosage according to a continuous schedule having a dosing interval of once weekly.

In short, neither the patent specification nor the testimony of any witness supports the district court’s holding that in claims 23 and 37 the word “about” has any meaning other than its ordinary meaning of “approximately.” The district court’s claim construction is erroneous.

B. Claims 23 and 37, Correctly Construed, are Anticipated by the July 1996 *Lunar News*

Merck stipulated that it would not assert a date of invention before July 22, 1997 (A93), the filing date of its earliest provisional application. The July 1996 *Lunar News* is therefore prior art under 35 U.S.C. § 102(a), because it was published before the patented invention was made.

Claim 23 defines a method of treating osteoporosis which comprises orally administering about 70 mg alendronate monosodium trihydrate, on an active alendronic acid basis, once-weekly. The July 1996 *Lunar News*

expressly discloses each of these elements. It discusses the use of bisphosphonates, including alendronate, in “dealing with osteoporosis,” which, as Merck never disputed, means both treatment and prevention of osteoporosis. (A66; A231). That publication also makes clear that the alendronate therapy it is discussing includes “oral” administration. It identifies alendronate as “Fosamax by Merck,” the active ingredient of which was well known to be alendronate monosodium trihydrate. Moreover, Fosamax dosage strengths were known to be reported on an alendronic acid basis. (A2841; A2845; A232-33). Finally, the article explicitly states that the drug can be administered on a weekly basis at a dose of 80 mg: “. . . oral alendronate potentially could be given in a 40 or 80 mg dose once/week.”

With respect to whether “about 70 mg” and “about 35 mg” encompass 80 mg and 40 mg, respectively, this Court’s precedents make clear that “about” must be afforded reasonable scope to encompass what persons skilled in the art would understand to be covered by the term. *See Modine Mfg. Co. v. United States Int’l Trade Comm’n*, 75 F.3d 1545, 1554, 37 USPQ2d 1609, 1615 (Fed. Cir. 1996):

Such broad usages as “about” must be given reasonable scope; they must be viewed by the decision-maker as they would be understood by persons experienced in the field of the invention.

See also Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed. Cir. 1995) (“The use of the word ‘about’ avoids a strict numerical boundary to the specified parameter.”).

The uncontradicted testimony of “persons experienced in the field of the invention” makes clear that “about 70 mg” and “about 35 mg” encompasses 80 mg and 40 mg, respectively, because 80 mg once/week is clinically very close to if not indistinguishable from 70 mg once weekly. (See *e.g.*, A231-33; A4876-76.1). First, the absorption of the drug varies from patient to patient by as much as a factor of three, so that variation among patients taking the same dose would be greater than the difference between the two doses. (A213-14). In addition, the accepted range for drug bioequivalence is ± 20 percent, which is greater than the difference between 80 mg and 70 mg. (A436-37). Third, Dr. Russell, perhaps the world’s leading expert on bone disease, testified that the doses would be essentially indistinguishable, and that any difference between them could only possibly be discerned by conducting an enormous study. (A436). Fourth, Dr. Santora, one of the inventors on the ’329 patent, confirmed that the doses were similar, stating that in his opinion 80 mg per week would be “similarly effective” to a 10 mg daily dose because “80 milligrams is approximately 7 times 10 milligrams.” (A4876-76.1). Fifth, Merck’s own scientists treated a

70 mg and an 80 mg weekly dose as clinically equivalent. (A1630, A1653). Finally, Merck's expert agreed that 80 mg once per week would be safe and effective for treatment of osteoporosis. (A764-65; A770-72). For these reasons, in light of the ordinary meaning of "about" as "approximately," there is no room to argue, and no Merck witness ever asserted, that 80 mg once-weekly is not "about 70 mg" once-weekly.

Similarly, claim 37 specifies a method of "preventing" osteoporosis by orally administering "about 35 mg" alendronate monosodium trihydrate once-weekly. The only difference between the two claims is that claim 23 is directed to "treatment" with an "about 70 mg" weekly dose and claim 37 is directed to "prevention" with an "about 35 mg" weekly dose. First, to a person skilled in the art, it is undisputed that the *Lunar News*'s reference to "dealing with" osteoporosis is a reference to both treatment and prevention. (A230-34), and the district court found that the *Lunar News* discloses treatment and prevention. (A66). Second, Merck never disputed that administration of 40 mg would have virtually the same therapeutic effect as administration of 35 mg. In fact, inventor Dr. Santora testified that for prevention of osteoporosis, a 40 mg weekly dose is "approximately seven times the daily dose," and would be "similarly effective to a 5 mg daily dose" for the prevention of osteoporosis. (A4865; A4876). Thus, according

to its “ordinary meaning,” “about 35 mg” once-weekly encompasses 40 mg once-weekly. (A234).

The July 1996 *Lunar News* therefore anticipates the claimed invention. The following chart makes clear the one-to-one correspondence between the *Lunar News* disclosure and claims 23 and 37.

Claim 23	Claim 37	July 1996 <i>Lunar News</i>
A method of treating osteoporosis in a human comprising	A method of preventing osteoporosis in a human comprising	The subject of the article is the use of bisphosphonates in “ <i>dealing with osteoporosis</i> ” in humans. (A3102). Dealing with osteoporosis includes both prevention and treatment of osteoporosis. (A234). The district court found that <i>Lunar News</i> discloses treatment and prevention. (A66).
orally administering		“ <i>Even oral alendronate potentially could be given...</i> ” (A3102; A231).
about 70 mg	about 35 mg	“... <i>in a 40 or 80 mg ...</i> ” (A3102). Eighty milligrams is “about 70 mg” because for practical purposes the doses are the same, and clinically would have the same effect on patients. (A231-32). Similarly, 40 mg is “about 35 mg”. (A234-35).
of alendronate monosodium trihydrate		The article identifies alendronate as “ <i>Fosamax by Merck,</i> ” the active ingredient of which is alendronate monosodium trihydrate. (A3102; A232).
on an alendronic acid basis		Fosamax dosage strengths are reported on an alendronic acid basis. (A2840-41, A2845).
as a unit dosage		“... <i>dose ...</i> ” (A3102; A233).
according to a continuous schedule having a dosing interval of once-weekly		“... <i>once/week ...</i> ” (A3102; A233).

The district court's finding that the *Lunar News* did not anticipate the claimed invention was based solely on its construction of the claim terms "about 70 mg" and "about 35 mg." (A42). The district court did not find that 80 mg once-weekly was not "approximately" 70 mg once-weekly. Instead, following its own flawed construction, it considered whether the 70 mg and 80 mg were the same, and, not surprisingly, found that they were not. This finding is irrelevant, as is the district court's reference to the statutory requirement that the dosage strength of a generic drug be the same as that of the listed drug. *See* 21 U.S.C. § 355(j)(2)(A)(III). (A42). The statute requires that the dosages of the generic and the listed drugs must be "the same." The claim term, on the other hand, expressly eschews exactitude, requiring only that the dosage be "about 70 mg." Similarly misplaced is the district court's observation that Teva "provided no . . . data" to demonstrate that 80 mg weekly and 40 mg weekly are the "same" as 70 mg and 35 mg weekly, respectively. (A42). The evidence was undisputed that the two corresponding doses were approximately equal in clinical effect,

which is all the claim requires. The district court's finding that Teva had not shown that 80 mg weekly is "the same" as 70 mg is thus irrelevant.⁶

Finally, the district court also referred to "inherency," finding that Teva's "inherency" argument failed. (A39). Teva, however, never argued that the *Lunar News* "inherently" anticipated the claims. On the contrary, the *Lunar News* expressly anticipates the claimed invention because to a person skilled in the art "about 70 mg" once per week expressly encompasses 80 mg. For that reason, the district court's discussion of inherency is inapposite.

The district court's anticipation holding is based solely on a legal error – its construction of "about." Accordingly, that holding should be reversed and claims 23 and 37 held invalid.

⁶ The district court stated that it would not address "enablement of the prior art." (A44). However, there is no issue that the prior art is enabling. Inventor Dr. Santora testified that creating the once-weekly dosage form was "trivial," and presented "no technology issue." (A4865; A4867-68).

III. THE DISTRICT COURT ERRED IN HOLDING THAT THE CLAIMED INVENTION WOULD NOT HAVE BEEN OBVIOUS

A. Administration of Alendronate Once-Weekly Admittedly was “Known” to Those Skilled in the Art

As the district court found, based on Merck’s admission, weekly administration of alendronate for treatment and prevention of osteoporosis was known before July 1997 to persons skilled in the art:

At the outset, the Court notes that Merck has never disputed that it was known that once-weekly dosing would be efficacious in providing the alendronate sodium needed to inhibit bone resorption.

(A59). Moreover, Merck’s and Teva’s experts agreed that as of July 1997 a person skilled in the art would have concluded that the appropriate once-weekly doses of alendronate to treat and prevent osteoporosis is 70 mg and 35 mg, respectively. (A238-39; A643-44; A776-78). Thus, the evaluation of the validity of the ’329 patent begins with the understanding that prior to July 1997 the invention of claims 23 and 37 of the patent — treating and preventing osteoporosis using weekly doses of 70 mg and 35 mg of alendronate sodium — was disclosed in the prior art. The ’329 patent therefore removes knowledge from the art, rather than adding knowledge to it. This a patent cannot do:

Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public, or to restrict free access to materials already available to the public.

Graham., 383 U.S. at 6, 148 USPQ at 462. Nowhere did either Merck or the district court identify a single contribution that the claimed invention made to the art. Instead, the '329 patent takes what was already known and makes it the exclusive property of Merck. Accordingly, the district court's holding that the claims are not invalid for obviousness is wrong.

B. The District Court Failed To Analyze the Claims under the Correct Standard

The district court's paradoxical decision to endorse a patent on what it found was already "known" or apparent to those skilled in the art resulted from its failure to apply the correct obviousness analysis. A patent claim is invalid "if the differences between the subject matter to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103. Thus, the focus is whether the claimed invention ("the subject matter to be patented") would have been obvious in the art in light of the differences between the prior art and what is claimed. *See Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 808, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989) ("the proper focus of an obviousness inquiry is on whether 'the differences between the subject matter sought to be patented and the

prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. . . .” (emphasis added)); *see also In re Woodruff*, 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935-36 (Fed. Cir. 1990) (“We first look to determine the differences between the claimed invention and the prior art.”).

While paying lip service to the statutory analysis, the district court did not follow it. Instead of analyzing the differences between the claimed invention and the prior art, the district court discounted the principal prior art references in their entirety, and upheld Merck’s patent that claimed precisely the same idea disclosed in them.

C. Analyzed under the Correct Standard, Claims 23 and 37 Are Invalid for Obviousness

The only differences the district court found between the *Lunar News* disclosures and the claimed invention are that the claims require the administration of “about 70 mg” or “about 35 mg” of alendronate weekly and the *Lunar News* is either silent regarding the dose (April 1996), or it teaches the administration of 80 mg or 40 mg weekly (July 1996). Of course, if the district court was wrong when it held that 80 mg and 40 mg are not “about 70 mg” and “about 35 mg,” then that sole difference disappears and the claims are anticipated. *See* section II, *supra*.

Thus, the correct inquiry here, assuming the district court's claim construction is correct, is whether administering 70 mg or 35 mg of alendronate once-weekly for treatment and prevention of osteoporosis would have been obvious in light of the difference between the prior art and the claim — between employing 80 mg instead of 70 mg and 40 mg instead of 35 mg. The district court never carried out this analysis.

In fact, no one disputed that persons skilled in the art would have recognized that the appropriate once-weekly doses are 70 mg and 35 mg for treatment and prevention of osteoporosis. Teva's expert explained the scientific rationale for that dose, testifying that the literature at the time taught that the total dose of alendronate administered over time, and not the frequency of dosing, determines alendronate's effect on bone resorption. (A239-40; A1348-56 at 1353). Thus, a person skilled in the art would have expected 70 mg once-weekly to have the same effect on bone resorption as 10 mg daily. (A240-47; A643-44). In addition, oral absorption of alendronate was known at that time to be linear between doses of 5 mg and 80 mg; thus the skilled person would have expected the same proportion of the dose of alendronate to be absorbed whether the drug was administered as seven smaller doses or a single larger dose. (A241-42; A1031). The only reason the *Lunar News* refers to 80 mg and 40 mg instead of 70 mg and 35

mg is that at the time Merck was offering a 40 mg tablet for treatment of Paget's disease, and 35 mg and 70 mg dosage strengths were not available. (A235-36; A765-66).

Merck offered no contrary evidence. In fact, its expert conceded that a person skilled in the art would have chosen 70 mg and 35 mg as the weekly doses. (A776-78; *see also*, A643-44). Thus, there is no issue about the appropriate dose that persons skilled in the art would have used in following the *Lunar News* once-weekly teaching.

In addition, Merck offered no evidence that the claimed dosages offer unexpected results. Merck's expert admitted that the July 1996 *Lunar News* discloses a safe and effective dosing regimen (A764-65, A770-72), and Merck offered no evidence that the claimed invention (70/35 mg once per week) exhibits any unexpected or superior properties compared to the *Lunar News* teachings (80/40 mg once per week). *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483, 44 USPQ2d 1181, 1186-87 (Fed. Cir. 1997). On the contrary, the claimed invention offers the same results taught by the *Lunar News*, an equally effective and more convenient dosing regimen.

D. The District Court's Bases for Rejecting the *Lunar News* Are Irrelevant

In rejecting Teva's obviousness defense, the district court did not reject the *Lunar News* disclosures because they failed to suggest the claimed invention. Instead, the court held that the articles were not "clinically useful" because of "known dose-related gastrointestinal side effects," and that because they were not published in peer-reviewed journals or authored by a person with the appropriate graduate degree, they did not overcome the "serious side effect concerns associated with higher dosage units of alendronate sodium." (A66). With respect to the *Lunar News* disclosures, the court concluded:

First the April 1997 [sic, 1996] *Lunar News* did not deal with the specific dosages of 70 or 35 mg in relation to its discussion of once-weekly dosing of alendronate. Second, the July 1996 *Lunar News* listed 40 and 80 as compared to 70 and 35 mg dosages as suggested by the '329 Patent and did not deal with the problem of known gastrointestinal side effects. Additionally, in reaching its conclusion, the Court gives more weight to the prior art references written and reviewed by those skilled in the art such as the Chestnut [sic] study and the De Groen case report as opposed to the *Lunar News*, a quarterly newsletter written by someone without a Ph.D. or M.D. in the applicable field.

(A68). Thus, the district court's rationale for discounting the *Lunar News* boils down to the following:

- The April and July 1996 *Lunar News* articles do not disclose the administration of 70 mg or 35 mg of alendronate.
- Neither the April 1996 nor the July 1996 *Lunar News* “deal with” the “known” gastrointestinal side effects allegedly described elsewhere.
- The *Lunar News* is entitled to no weight because of 1) the nature of the publication, and 2) the credentials of its author.

The court cited no authority supporting the rejection of *Lunar News* prior art. Those publications are prior art for all that they disclose and fairly suggest. *See e.g., In re Oelrich*, 579 F.2d 86, 91, 198 USPQ 210, 214 (CCPA 1978) (“statements appearing in the prior art literature are good, for purposes of rejection under § 103, for all that they would fairly suggest to one of ordinary skill in the art”); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976); *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983). A court may not simply ignore a prior art reference. Instead, the court must analyze the obviousness of the claimed invention in light of the differences between the prior art and the claimed invention.

1. Whether the April And July 1996 *Lunar News* Articles Expressly Disclose Administration of “70 Mg” and “35 Mg” Is Irrelevant

In asserting that the April and July 1996 *Lunar News* references do not expressly disclose the dosage limitations of claims 23 and 37 (under the district court’s erroneous claim construction), the district court confused obviousness with anticipation. This Court has repeatedly held that the prior art need not disclose every limitation in order to render a claimed invention obvious under section 103:

[T]he mere absence from the prior art of a teaching or a limitation recited in the patent at issue is insufficient for a conclusion of nonobviousness. Unlike a section 102 defense which requires that a single reference describe each and every element of a claimed invention . . . , “the question under 35 USC 103 is not merely what the references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made.”

Merck, 874 F.2d at 807-808, 10 USPQ2d at 1846 (internal citations omitted); *see also Sibia Neurosciences*, 225 F.3d at 1357, 55 USPQ2d at 1932; *In re Huang*, 100 F.3d 135, 138, 40 USPQ2d 1685, 1688 (Fed. Cir. 1996) (refusing to read unclaimed features into claims for purposes of determining validity). Merck conceded that persons skilled in the art would have selected 70 mg and 35 mg (A643-44; A776-78), that the 80 mg and 40 mg doses in the *Lunar News* represented a recognition of the reality that 40 mg tablets were commercially available at the time (A765-66), and that the

clinical differences between 70/35 and 80/40 were negligible. The fact that the *Lunar News* does not expressly disclose 70 mg and 35 mg dosages is therefore irrelevant to the determination of obviousness, and the district court's reliance on this fact was misplaced.

**2. Whether the *Lunar News* “Deals With”
Gastrointestinal Side Effects Is Irrelevant**

In its reasons for finding the claimed invention nonobvious, the district court stated that the April and July 1996 *Lunar News* do not “deal with the problem of known gastrointestinal side effects.” (A68).

First, this statement is not true. For example, the April 1996 *Lunar News* refers to the upper gastrointestinal distress patients may suffer if they fail to follow the dosing instructions (A3066), and the July article discusses physicians' experiences and the rare cases of severe distress. (A3102).

Setting that factual error aside, however, the court's statement has no bearing on whether the claims are patentable. The court never explains what it meant by “deal with . . . side effects.” The claimed invention is not about side effects. The claims are for the treatment and prevention of osteoporosis; they say nothing about side effects, known or otherwise. In fact, Merck originally claimed the amelioration of side effects, but cancelled those claims during prosecution. (A1830; 1859-64).

When Dr. Mazess published the *Lunar News*, he disclosed to the public a safe and effective dosing regimen for treatment and prevention of osteoporosis. Whether others would have been skeptical of the safety of that regimen at the time Dr. Mazess disclosed it is beside the point. Irrespective of whether Merck's inventors proceeded contrary to some conventional wisdom about side effects, they were not the first to do so. Dr. Mazess had the same insight and placed it in the public domain before Merck's inventors had the idea. Merck cannot patent what Dr. Mazess had previously chosen to disclose to the public. If a skepticism existed, the person entitled to credit for first seeing past it was Dr. Mazess, not Merck's inventors, who had the same idea a year later. Even if others skilled in the art would have been skeptical of Dr. Mazess's insight at the time he expressed it, the fact remains that because he was first, his disclosure is part of the prior art and cannot be disregarded.

Moreover, Merck's inventors cannot even take credit for proving that Dr. Mazess's earlier insight was sound. Before they filed for the '329 patent they did no clinical research or other testing in humans. (A642-44). Thus, they added nothing to the art that was not already set forth in the *Lunar News*. The only data in the patent was generated in beagles whose esophagi were soaked in alendronate solutions for extended periods. The author of

those data thought they were irrelevant to human experience (A4854; A4859-60; A4862), they were discredited at trial and the district court correctly disregarded them.

Even assuming that the skepticism existed, and assuming that Merck's inventors had made the observation that larger weekly doses were not associated with the feared gastrointestinal side effects, these facts cannot make patentable the method already taught by the *Lunar News*. In both the anticipation and obviousness contexts, this Court has held that the discovery of previously unrecognized properties inherent in the prior art cannot support a patent claim covering either that prior art, or what was obvious from it. *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1667 (Fed. Cir. 2003) (anticipation – prior art compound inherent in disclosed method); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351, 64 USPQ2d 1202, 1206 (Fed. Cir. 2002) (anticipation – method of preparing sprouts rich in certain enzymes inherent in prior art cultivation and preparation of the same product); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (anticipation – method of hair depilation inherent in prior art skin treatment that disrupted hair follicles); *Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936 (obviousness – “[i]t is a general rule that merely discovering and

claiming a new benefit of an *old* process cannot render the process again patentable.) (emphasis in original); *In re Baxter Travenol Laboratories*, 952 F.2d 388, 392, 21 USPQ2d 1281, 1284 (Fed. Cir. 1991) (obviousness – “[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention.”); *In re Wiseman*, 596 F.2d 1019, 1023, 201 USPQ 658, 661 (CCPA 1979) (obviousness – “[applicants] are, in effect, arguing that a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable to them because it also possesses an inherent, but hitherto unknown, function which they claim to have discovered. This is not the law.”). Here, the side effects (or absence thereof) of administering weekly doses of alendronate to treat and prevent osteoporosis are inherent in carrying out the method taught by the *Lunar News*. Thus, whether analyzed under section 102 or section 103, the observation of those side effects cannot make Merck’s claims patentable.⁷

⁷ Nor can it be said that the prior art “teaches away” from the claimed invention. “A reference may be said to teach away when a person of ordinary skill, upon reading *the reference*, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994). The *Lunar News* articles do not teach away from using 70 mg or 35 mg of alendronate once-weekly; on the contrary, they encourage it and explain its advantages.

3. **The District Court Erred in Discarding the *Lunar News* Based on its Author's Pedigree**

Remarkably, the district court brushed aside the teachings of the *Lunar News* because it was “a quarterly newsletter written by someone without a Ph.D. or M.D. in the applicable field.”⁸ (A68). The district court cites no authority for the proposition that the prior art can be rejected because the author did not go to the right schools. In addition, section 102 makes no such distinctions between classes of publications; it requires only that a reference be “a printed publication.” The district court’s failure to analyze the disclosure of the *Lunar News* on this basis was error.

E. The District Court’s Findings About the Expectation of Gastrointestinal Side Effects are Clearly Erroneous

The district court’s holding that the *Lunar News* articles would not have made the claimed invention obvious was based on the conclusion that the prior art gave rise to an expectation of increased gastrointestinal side effects which the *Lunar News* did not “deal with.” As discussed above, the

⁸ The district court’s refusal to give Dr. Mazess any credit for his three decades of work in osteoporosis and his pioneering status in the field is inexplicable. Dr. Mazess’s deposition outlined his credentials (A4822-36), and Merck presented no evidence to undermine them, aside from denigrating his graduate studies because they were in “anthropology.” Even a cursory reading of Dr. Mazess’s deposition puts the lie to any perception that he was unqualified to offer an opinion on an osteoporosis-related topic. However, the Court need not address this issue to reverse the district court’s decision on obviousness, because Dr. Mazess’s credentials are irrelevant.

district court's reasoning is flawed – whether the *Lunar News* “deal[s] with” side effects is irrelevant. Thus, even if the district court's factual findings on “side effects” were correct, this Court need not find clear error in those findings to reverse its ultimate decision on obviousness. *See e.g., Merck, supra*, 874 F.2d at 807, 10 USPQ2d at 1845 (“We do not quarrel with the factual findings of the district court, but we believe its conclusion that obviousness had not been proven is incorrect as a matter of law.”).

In any event, however, the district court's holding fails on its own terms, and its findings of fact with respect to the “fear defense” are clearly erroneous. Indeed, every act or statement made by or on behalf of Merck before this litigation provided a motive to say otherwise makes clear that the “fear” of increasing gastrointestinal side effects from weekly doses of alendronate did not exist.

1. The District Court's Finding of an Expectation of Increasing Gastrointestinal Side Effects With Weekly Doses of Alendronate is Clearly Erroneous

Shortly after Merck's launch of daily 10 mg alendronate in late 1995, occasional reports appeared in the literature of individual cases of severe esophagitis associated with the administration of Merck's 5 mg and 10 mg alendronate products. These cases were extremely rare; for example, by March 1996, a half-million patients had been prescribed alendronate, and

only 50 serious esophagitis cases (one in every 10,000 patients) had been reported. (A1048-54 at 1050; A531). Although Merck initially took no action in response to these reports, eventually it investigated the issue and determined that in a majority of the cases the problem was associated with the failure of patients to follow the dosing instructions. (A4803; A4815-16). This failure led to incidents of tablets “sticking” in the esophagi of some patients and causing ulceration. (A373-74; A536-38; A1048-54 at 1048; A2364-65; A4803; A4817-20). Based on its analysis of the issue, in March 1996 Merck issued a “Dear Doctor” letter addressing the esophagitis cases and advising reinforcement of the dosing instructions. (A1289-90).

Merck’s letter worked. Following its distribution, the reported incidence of serious gastrointestinal side effects fell to almost nothing long before the ’329 invention date. Although Merck argued, and the district court accepted, that these reports sent shockwaves through the medical community, in fact, they did not produce even a ripple in Merck’s sales. Between March 1996, the date of Merck’s Dear Doctor letter, and October 1996, the number of patients being prescribed alendronate doubled from 500,000 to one million. (Compare A1750, A1755 to A2866, A2876). Likewise, Merck’s sales grew 72 percent between 1996 and 1997. (A2704-

5). Thus, it can hardly be said that these case reports were a significant worry in the medical community.

In October 1996, Merck reported the severe esophagitis cases in an article by De Groen in the New England Journal of Medicine. (A1048-54). Both parties' experts agreed that the data suggested that the cause of the severe esophagitis cases was "pill esophagitis," i.e., ulceration caused by the tablet sticking, most often as a result of failure to follow the dosing instructions. (A287; A377-78; A530; A533).

Contrary to the district court's finding, these severe esophagitis reports would not have deterred a person of skill in the art from administering weekly doses of alendronate. First, the incidents were very rare. None of the experts testifying at trial had ever seen one. Indeed, in March 1996, Merck told the FDA that the incidence of the reported severe esophagitis cases did not rise to the number expected in the treated population. (A1750-54, A1770). Second, there was no evidence in the severe esophagitis cases of dose-relatedness. (A4803; A4810-11). To the contrary, some of the cases reported in the literature and relied on by the district court involved administration of the 5 mg tablet, Merck's lowest dosage. The literature suggested that these reports were attributable, not to large doses, but "repeated" doses. (A3836). Finally, the evidence at trial

demonstrated that weekly administration of alendronate would have been expected to *decrease* the incidence of gastrointestinal side effects because it would 1) improve patient compliance with the dosage instructions, and 2) decrease the frequency of tablet administration, thereby decreasing the chances of a tablet “sticking” in the esophagus. (A290-91; A538).

As the district court found, the only reference in evidence concerning the administration of higher doses of alendronate to osteoporosis patients was the Chesnut paper. (A1102-10). This reference was the linchpin of Merck’s entire case, and it is likewise the centerpiece of the district court’s opinion. However, Chesnut does not teach that weekly dosing of alendronate would be expected to be poorly tolerated, and it certainly does not suggest that no patient would be able to tolerate a weekly dose of alendronate. Indeed, before this litigation gave it the incentive to argue the contrary, Merck relied on the Chesnut study as *supporting* the idea of weekly dosing.

In Chesnut, seven out of 63 post-menopausal osteoporotic women taking 40 mg per day dropped out of the study because of mild gastrointestinal side effects, compared with smaller percentages of dropouts

in the groups taking lower doses of alendronate.⁹ (A1108). Dr. Chesnut and his co-authors (which included Dr. Santora, one of Merck's inventors) drew no conclusions regarding the statistical significance of the reported results. However, the district court accepted Merck's revisionist portrayal of Chesnut, relying on the reference to find a "clearly documented and known dose related gastrointestinal side effects associated with high doses (over 20 mg) of oral alendronate." (A67-68). Based on this, the district court rejected the *Lunar News* articles relied on by Teva. This finding is clearly erroneous.

First, as Merck admitted by Merck in its pre-litigation documents, Chesnut demonstrates that 90 percent of post-menopausal osteoporotic women tolerated the 40 mg *daily* dose. Chesnut provides no information regarding weekly dosing. Moreover, even assuming that 70 mg weekly resulted in the 11 percent dropout rate to which the district court referred, that rate would be acceptable. Merck's expert testified that in his practice 10-12 percent of patients on 10 mg alendronate daily discontinue due to mild gastrointestinal upset. However, he continues to prescribe the product,

⁹ Although Merck has attempted to meld the two, the mild side effects referenced in Chesnut are not related in any way to the serious esophageal ulceration seen in patients who do not follow the alendronate dosing instructions. (A701).

demonstrating the acceptability of such an incidence of these side effects. (A745-46). Thus, standing alone, the Chesnut paper would not have deterred a person of skill in the art from administering 70 mg alendronate once-weekly. (A545-46). In fact, Merck relied on Chesnut before the FDA to support its proposed once-weekly dosing regimen. (A1726). Thus, Chesnut provides a “reasonable expectation” of success. *In re O’Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986). As described below, that is precisely the position taken by Merck prior to this litigation. The district court’s contrary conclusion is clearly erroneous.

2. The District Court’s Rejection of the Paget’s Disease Experience was Clearly Erroneous

In order to come to the conclusion that a skepticism existed in the prior art regarding the administration of “larger” doses of alendronate sodium, the district court rejected as irrelevant all of the evidence concerning Paget’s patients. This finding was clearly erroneous.

As discussed above, Paget’s disease is a common bone disease characterized by increased bone resorption. Teva presented evidence at trial that prior to July 1997 Paget’s patients had been given up to 80 mg of alendronate *daily* for six months without unacceptable side effects. This evidence clearly belies Merck’s argument that persons of skill in the art

would have been skeptical of 70 mg *weekly* doses prior to July 1997.

However, the district court rejected this evidence because, according to the court, it was “well known” that “patients with Paget’s disease tolerate higher doses of alendronate than patients with osteoporosis.” (A65, n.8). Based on this finding, the district court refused to address studies dealing with Paget’s disease. However, prior to this litigation, Merck took precisely the opposite position.

The Paget’s disease evidence included 1996 papers co-authored by Merck’s inventor, Dr. Yates. In both of those papers (Siris and Reid), the authors conclude that 40 mg of alendronate administered *daily* for 6 months was “well tolerated.” (A1111-19 at 1115; A272; A2293-2300 at 2297; A269). In addition to these studies, thousands of Paget’s patients had taken Merck’s 40 mg tablet prior to July 1997 with acceptable side effects. (A1050; A266-67; A3450-69 at 3455). Finally, a 1997 paper by Khan, which compared the side effect profiles of 40 mg daily and 80 mg daily for six months, reported no apparent dose response between 40 mg and 80 mg in terms of gastrointestinal side effects. (A2417-2426 at 2423; A1726).

The data from the Paget’s studies demonstrates that 40 mg and 80 mg of alendronate *daily* were well-tolerated, and that 40 mg daily was as well tolerated as placebo. In addition, by 1997, thousands of Paget’s patients had

taken the 40 mg daily dose clinically, with no greater degree of gastrointestinal complaints or severe complications. (A266-67; A3450, A3455). Thus, the Paget's disease data provided compelling evidence that the once-weekly dose of 70 mg alendronate would have been well tolerated.

Merck hatched a story for trial that the data generated in studies of Paget's patients cannot be used to draw conclusions regarding the tolerability of the drug in osteoporotic patients, and thus is irrelevant to the invention of claims 23 and 37 of the '329 patent. The district court adopted Merck's position. However, before this litigation provided Merck with a motive to adopt this story, its position, both internally and externally, was consistently the opposite.

Internally, in a May 20, 1997 "Tactical PAC" review seeking management approval to go forward with a once-weekly dosing program, Merck's scientists relied on the Paget's data to support the expected tolerability of the higher once-weekly dosing regimen *for osteoporosis*. (A1630, 1653). Merck's own analysis confirmed that the Paget's data supported the safety of the proposed regimen:

There is human safety data available on these higher doses. The largest experience is derived from the Paget's Disease studies including data on over 150 patients randomized to receive 3-6 months of daily treatment with alendronate 40 or 80 mg. This data is supplemented by short term clinical pharmacology studies with doses up to 100 mg. In all theses

[sic] studies, *the 40 and 80 mg doses were well tolerated* even when given on a daily basis, although daily treatment with alendronate 40 mg was associated with a moderate increase in upper GI adverse events in the Phase II study of treatment of osteoporosis (Protocol 026).

(*Id.*) (emphasis added). In view of the Paget's data, Merck did not regard tolerability as a significant concern. To the contrary, Merck's scientists stated that higher once-weekly dosing would be "unlikely to have a greater potential to induce upper GI irritation." (*Id.*). Indeed, the only concerns Merck had were economic: (1) whether a patent could be obtained for once-weekly dosing to "allow for extension of the FOSAMAX patent to 2018," and (2) the potential negative impact of once-weekly dosing on "pricing." (*Id.*).

Externally, in a March 1998 formal submission to the FDA regarding weekly administration of alendronate for *osteoporosis*, Merck maintained the position earlier taken internally that the data from Paget's disease studies provides an expectation that a once-weekly dose would be well-tolerated:

Experience in Paget's disease (up to 80 mg alendronate for 6 months) suggests that dosing regimens of either 35 or 70 mg weekly, and 35 mg twice-weekly should be *well-tolerated*.

(A1711-14, A1735; emphasis added).

Elsewhere in that same document, Merck drew both on the Paget's data and the data from Chesnut in concluding that a once-weekly dose for osteoporosis should be "very well-tolerated":

Oral doses of alendronate up to 80 mg daily for up to six months have been well-tolerated in patients with Paget's disease, and approximately 90% of postmenopausal patients with osteoporosis remained on alendronate treatment at 40 mg daily for one year. *Thus, alendronate dosing regimens of either 35 or 70 mg once-weekly, and 35 mg twice weekly should be very well-tolerated.*

(A1726; emphasis added). Slides for the FDA presentation held a few weeks later reiterated that "Evidence for Safety" was found in the Paget's studies where patients were treated with "80 mg/day for 3 to 6 months in 42 patients with good tolerability . . ." (A3427; A3455). In that same slide, it is noted that there had been "[f]ew reports of UGI [upper gastrointestinal] AEs [adverse events] from marketed use of 40 mg." (*Id.*).

In 2000, all three inventors listed on the '329 patent co-authored a publication explaining the rationale for once-weekly dosing of alendronate in osteoporosis. (A1021-28). Under the heading "Safety and Tolerability Studies in Humans," the inventors once again cited the Paget's disease data as providing a "convincing" expectation that a once-weekly dosing regimen would be tolerated by osteoporotic patients:

Convincing human tolerability data for a higher dose of alendronate come from clinical trials of alendronate in the

treatment of Paget's disease. Treatment with 40 mg alendronate daily for up to 1 year was associated with tolerability profiles comparable to those of the control agent (placebo or etidronate), and no patient discontinued alendronate treatment due to a serious drug-related adverse event.

(*Id.* at 1028.1). As support for that proposition, the inventors cited the Paget's disease studies by Siris, Reid, and Khan discussed *supra*.

Thus, the district court's determination that the data from Paget's studies are irrelevant to the expectation regarding weekly dosing of alendronate in osteoporosis patients is completely undermined by Merck's own documents. Merck's pre-litigation documents, prepared for the most part by the inventors on the '329 patent, demonstrate that Merck believed the Paget's experience to be of central relevance in the question of the expected tolerability of once-weekly therapy with alendronate. The district court disregarded the Paget's data along with all of Merck's documents addressing those data.

Had the district court not erroneously adopted Merck's "fear defense," it would have had no choice to find the claimed invention obvious, even under its own flawed theory that the fear defense was relevant in this case. Thus, under both the correct analysis and under the district court's analysis (corrected for its erroneous fact-finding), the result is the same: claims 23 and 37 are invalid.

**F. The District Court Erred in Relying on Alleged
“Commercial Success” because any Success Cannot be
Attributed to the Unobviousness of the Invention**

**1. “Commercial Success” is Irrelevant Here because it Is
Unconnected with “Obviousness”**

The only “secondary consideration” on which the district court relied was “commercial success.” (A68). The court found that the invention was a “commercial success” primarily because sales of the weekly product increased over those of the daily product. The court found that Merck showed a “nexus” between the commercial success of the weekly product and the patented invention – that is, that the advantages of weekly dosing were in part responsible for an increase in sales. (A71).

The district court’s finding of fact, however, even if supported, does not demonstrate the kind of “commercial success” that bears on the obviousness inquiry under the patent laws. The district court failed to consider the threshold principle – the connection between commercial success and non-obviousness. The reason a court may consider the commercial success of an invention is that it may tend to show the existence of an economic incentive to make the contribution the invention made. The fact that despite this incentive, others skilled in the art did not make the invention may show that the invention was not obvious to them. *See*

Chicago Rawhide Mfg. Co. v. Crane Packing Co., 523 F.2d 452, 459, 187

USPQ 540, 546 (7th Cir. 1975), *cert. denied*, 423 U.S. 1091 (1976):

Commercial success demonstrates that there was a market for the patented device and implies that persons skilled in the art had an economic incentive to make it as soon as they could; the failure to produce a device satisfying a known demand indicates that the inventor's solution was not obvious.

See also Cosden Oil & Chem. Co. v. American Hoechst Corp., 543 F. Supp. 522, 541, 214 USPQ 244, 260 (D. Del. 1982); *Minnesota Mining & Mfg. Co. v. Research Medical, Inc.*, 679 F. Supp. 1037, 1054, 6 USPQ2d 1401, 1404 (D. Utah 1988) ("Commercial success is considered relevant to lack of obviousness on the rationale that competitors would have been economically motivated to make the invention sooner if it had been truly obvious.").

This rationale – the sole rationale for relating commercial success to non-obviousness – does not exist in this case. When Merck received FDA approval to offer daily alendronate in September 1995, two impediments existed that separately precluded anyone from competing with Merck. First, Merck had another patent, the '077 patent, which this Court has held covers the administration of alendronate sodium to treat osteoporosis. Second, when Merck received approval to market Fosamax, that approval came with the exclusive statutory right to be the only entity that could offer alendronate at *any* dosage strength for the next five years because alendronate was a new

chemical entity. *See* 21 U.S.C. § 355(c)(3)(D)(ii). For the first four of those years, the FDA would not even accept an alendronate application for filing for the indications approved for Fosamax, much less grant an approval.

Thus, no one had the incentive or even the ability to develop weekly dosage forms because only Merck could sell the drug in any form. Even if the advantages of weekly alendronate (which were disclosed in the prior art in July 1996) drove sales, that fact does not prove anything, because the insurmountable barriers to market entry represented by Merck's patent and other exclusivities prevented others from even attempting to compete.

The rationale discussed above must be considered to separate merely good ideas from those that are unobvious. The district court's finding that a "nexus" exists between the invention and the commercial success of the invention merely shows that once-weekly dosing was a good idea, not that it was unobvious. Carrying an umbrella when the forecast calls for rain is a good idea, but not an unobvious one. Indeed, the advantages of the invention – what made it a good idea – were disclosed in the prior art, but no one but Merck could take advantage of those disclosures. That Merck did so does not show that what Merck did was unobvious.

2. The Alleged “Commercial Success” Cannot Overcome the Showing of Obviousness

The alleged “commercial success” here was based on an incremental increase in sales of a drug, Fosamax, whose sales were already increasing dramatically even before the claimed invention was commercialized. Thus, the success is represented not by a product that displaced other products or created its own new market, but by a product that Merck substituted for an existing highly successful product. That the sales increased incrementally is hardly surprising in light of the advantages of the claimed invention – all of which were disclosed in the *Lunar News*.

It is well settled that commercial success cannot overcome a strong showing of obviousness. Here, the obviousness of the claimed invention is virtually conceded. The court found that the efficacy of weekly dosing was “known,” and the appropriate dose was apparent to those skilled in the art. The only reason for the district court’s holding with respect to obviousness is a misunderstanding of the correct obviousness inquiry and what facts are relevant to it. In this case, the obviousness evidence is strong, and “commercial success” is insufficient to overcome it. *See, e.g., EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907-908, 225 USPQ 20, 25-26 (Fed. Cir. 1985); *In re Inland Steel Co.*, 265 F.3d 1354, 1366, 60 USPQ2d 1396, 1406 (Fed. Cir. 2001); *Merck*, 874 F.2d at 809n.1, 10 USPQ2d at 1848n.1;

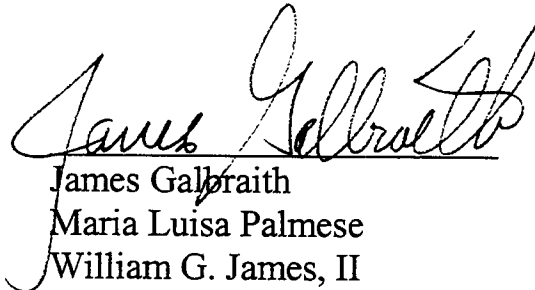
Ryko Mfg. Co. v. Nu-Star Inc., 950 F.2d 714, 719, 21 USPQ2d 1053, 1057-58 (Fed. Cir. 1991).

CONCLUSION

For the foregoing reasons, the district court's judgment should be reversed.

Respectively submitted,

December 17, 2003

A handwritten signature in black ink, appearing to read "James Galbraith", is written over a horizontal line.

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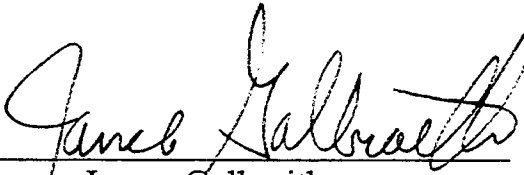
CERTIFICATE OF SERVICE

I hereby certify that on this date I served the foregoing Brief of Defendant-Appellant Teva Pharmaceuticals USA, Inc., on plaintiff-appellee Merck & Co. Inc., by causing two copies thereof to be delivered by overnight courier to

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of F.R.A.P. 32(a)(7)(C). This brief contains 13,985 words.

December 17, 2003

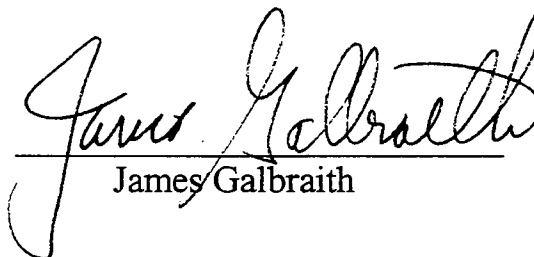

James Galbraith

EXHIBIT H

No. 04-1005

IN THE
United States Court of Appeals
FOR THE FEDERAL CIRCUIT

MERCK & CO., INC.,

Plaintiff-Appellee,

—v.—

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE IN CIVIL ACTION NO. 01-CV-0048,
JUDGE JOSEPH J. FARNAN, JR.

**REPLY BRIEF FOR DEFENDANT-APPELLANT
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**CERTIFICATE OF INTEREST FOR
TEVA PHARMACEUTICALS USA, INC.**

Counsel for defendant-appellant Teva Pharmaceuticals USA, Inc.,
certifies the following:

1. The full name of every party represented by me is:

Teva Pharmaceuticals USA, Inc.

2. The names of the real parties in interest represented by me are:

See response to number 1.

3. All parent corporations and any publicly held companies that
own 10 percent or more of the stock of the party represented by me are:

Teva Pharmaceuticals Europe B.V.
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4. The names of all law firms and the partners or associates that appeared for the parties represented by me in the trial court or are expected to appear in this Court are:

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INTRODUCTION

Merck seeks this Court's endorsement of its '329 patent despite Merck's failure to identify a single contribution that its inventors made over the prior art, in particular the prior art disclosures of the April and July 1996 issues of *Lunar News*. Merck does not contend that the claimed invention adds anything to those disclosures, but argues that the *Lunar News* should be ignored because doctors would not have believed that the methods the author proposed would be safe. It urges the Court to discard the *Lunar News* because it does not include data supporting the safety of once-weekly alendronate, while at the same time it argues that the absence of such data from the '329 patent is not a defect. (Red Br. 57 n.7). The district court's analysis and Merck's theory boil down to the claim that Merck is entitled to patent Dr. Mazess's original concept because by reason of his education and the forum in which he chose to publish it, he would not have been able to convince doctors to adopt it, whereas Merck was not laboring under that disadvantage.

Merck's theory is specious. The '329 patent claims nothing more than employing once-weekly dosing of alendronate to treat and prevent osteoporosis – exactly what the *Lunar News* taught. It does not claim anything about tolerability or side effects, and whether the *Lunar News*

includes data about that topic is irrelevant. Merck's theory of prior art nullification cannot be the law. Patent validity issues cannot turn on who has what graduate degree. A prior art publication directed to persons skilled in the art that teaches an invention cannot be disregarded because the later patent's inventors or their assignee enjoy a greater measure of scientific prestige.

I. THE JULY 1996 *LUNAR NEWS* ANTICIPATES CLAIMS 23 AND 37

A. Merck Relies Solely on the District Court's Claim Construction Error

The district court's failure to find that the July 1996 *Lunar News* anticipated claims 23 and 37 derives from its claim construction error. Although Merck disputes that the *Lunar News* discloses the dosage strengths recited in those claims, it concedes that it discloses every other element of the claimed invention. Thus, whether the district court's anticipation holding can stand reduces to a legal question, freely reviewable here: What is the correct construction of "about 70 mg" and "about 35 mg" in claims 23 and 37 — does it have what Merck concedes is its ordinary meaning of "approximately" or does it have a special meaning of "on an alendronic acid basis"?

Merck's special meaning argument is based on two sources: a passage from the specification that does not purport to define the disputed term, but instead defines "on an alendronic acid active basis," and an alleged "admission" by Dr. Russell with respect to that same passage. Merck's argument should be rejected and with it the district court's judgment based on that argument.

B. The Specification Does Not Include a "Clear Definition" of "About" Contrary to its Ordinary Meaning

Merck ignores the principle that any definition from a specification that purports to contradict the ordinary meaning of a term in a claim must clearly do so. *Texas Digital Sys. Inc. v. Telgenix, Inc.*, 308 F.3d 1193, 1204, 64 USPQ2d 1812, 1819 (Fed. Cir. 2002); *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1331, 59 USPQ2d 1401, 1407 (Fed. Cir. 2001). Here, Merck and the district court rely exclusively on a passage that does not state that it is defining "about." Indeed, nothing in the specification provides any hint that the patentee was redefining a common English word to have precisely the opposite of its ordinary English meaning of "approximately."

The passage on which Merck relies merely states that when the patent employs the phrase "about 70 mg" in relation to an alendronic acid salt or hydrate, the quantity is "calculated based on 70 mg of alendronic acid."

(A999-1019, col. 11, line 65-col. 12, line 8). Both parties agree that the reason for calculating the quantity in that way is to provide a common denominator by ensuring that regardless of which alendronate salt or hydrate is employed, the same number of active molecules will be provided. (Blue Br. 25; Red Br. 30). Thus, the point of the passage is the basis on which the quantity is *calculated*, not the definition of “about.”

Under Merck’s construction, “about” signals the absence of any possibility of variation, no matter how minor, an interpretation exactly opposite to its ordinary meaning. This result is absurd, and contrary to this Court’s articulated principles of claim construction. A departure from the ordinary meaning must be explicit to constitute lexicography by the patentee.

Merck also relies on an alleged “admission” by Teva’s expert with respect to that same passage. The question to which Dr. Russell responded was:

I understand, but it is what it says, and perhaps the person wanted to say if it’s a certain salt one, you might use 71, and if it’s a certain salt 2, you might use 73. Isn’t that what’s indicated in this?

(A435). Since the question was, to be charitable, less than clear, Dr. Russell’s appropriate response was “possibly.” The next question was, “But that’s what the definition says; right?” to which Dr. Russell replied, “That is

the definition as it's described in the patent." (*Id.*). The context does not make clear what the questioner was referring to or what Dr. Russell understood was the subject of the question. Dr. Russell never accepted the idea that "about 70 mg" meant "exactly 70 mg," and when asked the question directly he confirmed his view that the passage was defining "on an alendronic acid basis," and was not defining "about." (A499).

The district court erred in permitting this bizarre exchange over "a certain salt one," and "you might use 73" to override the ordinary meaning of "about."¹ The district court's error was particularly striking, since its definition makes no sense in the context of both the remainder of the specification and the claims themselves.

Although Merck asserts that the district court's construction was based on "intrinsic evidence" (Red Br. 35), Merck does not address the fact that in at least 15 different places, the specification employs both "about [70] mg" and "on an alendronic acid basis" to refer to the same dosage strength. (Blue Br. 26-27). This consistent use of two separate descriptors for the same dosage strength demonstrates that they must supply different

¹ Merck's principal inventor and two expert witnesses testified at trial, and its other two inventors provided deposition testimony. None of them endorsed Merck's construction of "about."

information. Otherwise one or the other would be superfluous. Merck's failure even to acknowledge this fact is a recognition that it cannot be squared with the district court's construction of "about."

Merck's only other reference to the specification is to point out that Examples 7 and 8 report the dosage strength to two decimal places. (Red Br. 32). Merck argues that this expressed precision is inconsistent with the ordinary meaning of "about." That in these examples the formulator happened to measure the quantities with equipment capable of such precision does not mean that "about" admits to no deviation from those particular values. Construed in accordance with its ordinary meaning, "about 70 mg" would permit a range of dosage strengths, even if each individually, like the quantities in Examples 7 and 8, was reported to a hundredth of a milligram.

Even more telling than Merck's disregard for the specification is its failure to address the fact that the district court's construction makes nonsense out of the claims. If, as the district court held, "about 70 mg" means nothing more than "70 mg on an alendronic acid basis," then the "about 70 mg" limitation becomes superfluous. (Blue Br. 28-29). Merck does not dispute that a construction that makes a claim limitation superfluous is wrong. It merely asserts that the district court's construction

“does not render superfluous” any limitation (Red. Br. 33), but offers no explanation of how the court’s construction avoids that result. Merck lamely attempts to distinguish the authorities Teva cites (Red Br. 33), but its distinctions are irrelevant, and Merck in fact does not dispute the proposition for which Teva cites those cases.

C. The July 1996 *Lunar News* Anticipates the Claims

Although Merck asserts that the district court found the evidence of anticipation “not credible” (Red Br. 37), in fact the court made no such finding. The district court’s premise for its rejection of Teva’s anticipation defense was its claim construction. None of its findings is applicable if that construction is wrong.

The district court did not accept Dr. Russell’s opinion because he did not demonstrate that the dosage strengths were “the same,” since “he did not take into account the Court’s construction of the term ‘about 70 mg’.” (A41-42). Similarly, Merck’s expert, Dr. Papapoulos, never testified that the 80 mg was not “about 70 mg” if “about” is given its ordinary meaning of “approximately.” Finally, both Merck and the district court relied on FDA statutory requirements for dosage strengths. (Red Br. 38). The FDA requires a generic version to have the “same” dosage strength as the listed drug. 21 U.S.C. § 355(j)(2)(A)(iii). There is no dispute that 80 mg is not the

“same” as 70 mg. The ’329 patent, however, is not an FDA regulation; it was deliberately drafted more broadly to include dosage strengths that are “about” or “approximately” 70 mg and 35 mg.

Thus, Merck’s argument entitled “The District Court Correctly Found That Teva Had No Evidence That Different Medicinal Doses Are the Same” (Red Br. 37-40) is beside the point. Teva never contended that a 70 mg dose and an 80 mg dose were the “same.” Under the correct claim construction, Teva bore no burden to show that the doses were “the same” or even that they were “equivalent.” Teva’s burden was to demonstrate that they were “about” the same, a burden that it met notwithstanding the district court’s failure to make any findings with respect to it. Every witness who addressed the issue, including Merck’s inventor Dr. Santora, testified that in the context of administration of alendronate for the treatment and prevention of osteoporosis, 80 mg is “approximately” 70 mg and 40 mg is “approximately” 35 mg.² (See Blue Br. 31-32; A231-33; A4876-76.1; A213-14; A436-37; A1630-33; A764-65; A770-72).

² Merck asserts that Dr. Santora did not testify that the two strengths were “the same.” (Red Br. 39). Merck again deliberately obfuscates the issue; Dr. Santora confirmed that the 80 mg was “approximately” 70 mg and that 40 mg was “approximately” 35 mg, as required by claims 23 and 37. (A4876-76.1).

The district court never weighed the evidence in light of the ordinary meaning of “about 70 mg” and “about 35 mg.” Merck points to no evidence that contradicts that offered by Teva that 70 mg and 35 mg are “approximately” 80 mg and 40 mg in the context of the claimed invention. Under the correct claim construction, *the Lunar News* clearly and convincingly anticipates claims 23 and 37. The district court’s judgment should be reversed.

D. The *Lunar News* Enables the Claimed Invention

Merck claims that the July 1996 *Lunar News* did not “enable” the practice of the claimed invention because it did not include information to show that the side effects would be acceptable. Merck thus proposes a new standard for such prior art: it must include clinical data to demonstrate that the claimed invention is safe. Merck, however, asserts that the ’329 patent, which likewise contains no human clinical or laboratory data, is excused from such a requirement. (Red Br. 57 n.7).

Merck cites no authority for such a double standard, and its argument ignores what enablement is. The statutory test for enablement of the prior art is essentially the same as that for a patent application. That is, the reference must describe how to “make and use the invention.” 35 U.S.C. § 112. *See In re Epstein*, 32 F.3d 1559, 1568, 31 USPQ2d 1817, 1823 (Fed.

Cir. 1994); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569, 7 USPQ2d 1057, 1063 (Fed. Cir. 1988). The description is directed to a person of ordinary skill in the art, and requires only that such a person be able to make and use the invention without undue experimentation. *See In re Wiggins*, 488 F.2d 538, 543, 179 USPQ 421, 424 (CCPA 1973) (“a reference describing an oil refinery need not describe how to make bolts and rivets to be considered ‘enabling.’”).³

Here, the invention is administering a particular dosage strength of a known, commercially available drug at a particular interval. The claimed invention is carried out by swallowing pills, and is enabled by a disclosure of doing so. The *Lunar News* contains such a disclosure. It describes alendronate dosage strengths, 80 mg and 40 mg, that were already available in the marketplace, and states that they should be administered “once/week.” Since 80 mg and 40 mg are “about” 70 mg and 35 mg, the *Lunar News* enabled patients to practice the invention by buying alendronate tablets

³ Merck relies on *In re Spada*, 911 F.2d 705, 15 USPQ 1655 (Fed. Cir. 1990), and *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (Red. Br. 43), neither of which supports Merck’s argument. In *Spada*, the issue was not enablement, but instead whether the reference sufficiently “describe[d]” the claimed invention. In *Donohue*, the Court held that enablement of the prior art did not require that the disclosure actually have been carried out.

already on the market, and taking one or two of them once a week instead of once a day. Even if the district court's construction of "about 70 mg" and "about 35 mg" were correct, the *Lunar News* would still enable the claimed invention. Although 70 mg and 35 mg dosage forms were not commercially available in July 1996, Merck admitted that making them would have been "trivial," and presented "no technology issue." (See Blue Br. 36 n.6; A4865; A4867-68).

Merck's incoherent argument that the disclosure does not enable the invention because others would have been skeptical of it is unsupported by any authority, including the cases on which Merck relies. In fact, this Court has made clear that a reference can enable and therefore anticipate a claimed invention even if the reference itself disparages the invention and would thus deter a person of ordinary skill in the art from practicing it. *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360-61, 47 USPQ2d 1516, 1521-22 (Fed. Cir.1998); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378, 58 USPQ2d 1508, 1515 (Fed. Cir. 2001). Here, the *Lunar News* not only taught the patented invention, it affirmatively encouraged others to carry it out. Merck's expert conceded that following the *Lunar News* would result in a safe and effective treatment for

osteoporosis. (A764-65; 770-72). That some doctors would have been skeptical is irrelevant to its status and effect as prior art.

In support of its non-enablement argument, Merck asserts that the *Lunar News* disclosure “did nothing more than speculate.” (Red Br. 43). First, the record does not support Merck’s characterization. Merck’s own expert testified that the July 1996 *Lunar News* was a “suggestion” to physicians to administer alendronate once per week, and the district court so found. (A761; A66). Indeed, as the district court noted, Merck never questioned that a person of ordinary skill in the art reading the *Lunar News* would know that once weekly dosing would be effective in treating and preventing osteoporosis. (A59).

Second, Merck is betrayed by the authority on which it relies. In *Bristol-Myers Squibb*, the claim for a drug dosing regimen included a specific limitation to “premedicating said patient with a medicament that reduces or eliminates hypersensitivity reactions.” The prior art reference disclosed administering the same drug, described the unsuccessful result, and noted the problem of “hypersensitivity reactions.” The reference then stated that “[f]urther studies are needed to see if pretreatment regimens, alternative schedules . . . or a reformulated preparation will permit the safe administration of the compound.” This suggestion to carry out a study to

determine whether “premedication” would be effective was held to be an enabling disclosure of the specific claimed step of “premedication.” 246 F.3d at 1378-80; 58 USPQ2d at 1515-16. *See also Ciba-Geigy Corp. v. Alza Corp.*, 864 F. Supp. 429, 33 USPQ 1018 (D.N.J. 1994), *aff’d in part and rev’d in part*, 37 USPQ2d 1337 (Fed. Cir. 1995) (nonprecedential) (statement in a letter to the editor that “another alternative *might be* transdermal application [of nicotine] much in the manner of nitroglycerine and scopolamine patches” (emphasis added) held to anticipate a claim to a transdermal nicotine patch). The July 1996 *Lunar News* is certainly much less speculative than the references in *Bristol-Myers Squibb* and *Ciba-Geigy*; it states positively that the proposed once-weekly regimen will “avoid dosing problems and reduce costs,” two distinct motivations for adopting it. (A3102). Of course, “avoid[ing] dosing problems” is the principal advantage touted for the invention claimed in the ’329 patent, filed for a year later.⁴

⁴ Merck also notes that in *Bristol-Myers Squibb*, this Court reversed the grant of summary judgment with respect to certain of the dependent claims at issue because it was unclear that the reference’s general disclosure was actually a disclosure of the specific pretreatment medications recited in them. (Red Br. 44-45). Contrary to Merck’s assertion, this holding, which is irrelevant here, had nothing to do with “enablement.”

Finally, Merck's real contention is not that the *Lunar News* is speculative, but that it "failed to address" the alleged "skepticism" doctors would have about the tolerability of once-weekly higher dose administration. Whether *Lunar News* in fact "failed to address" this concern or whether the concern even existed is irrelevant because the '329 patent makes no claim with respect to tolerability. A prior art reference need not extol the virtues of an invention to anticipate it. See *Bristol-Myers Squibb, supra*.

II. MERCK DOES NOT DEFEND THE DISTRICT COURT'S LEGAL ERRORS ON OBVIOUSNESS

In its opening brief, Teva demonstrated that the district court's approach to obviousness led to two errors. First, the district court dismissed the *Lunar News* disclosures instead of starting with their teachings. Second, the district court failed to analyze obviousness in view of the differences between the claimed invention and the prior art. By failing to follow the correct methodology, the district court reached the wrong result.

Merck never confronts these assignments of error because it has no answer to them. Instead, Merck focuses on the largely irrelevant facts making up Merck's litigation-inspired "fear defense." Merck recasts the facts as if the *Lunar News* references never existed, and as if Merck's inventors were the first to conceive of or disclose once-weekly

administration of alendronate for osteoporosis. But Merck was not first, and arguing that the *Lunar News* should not have been believed does not make it go away.

Teva's burden was to prove the facts demonstrating obviousness by clear and convincing evidence. Teva did so. It demonstrated the scope and content of the prior art: that the *Lunar News*, particularly the July 1996 issue, disclosed once-weekly administration of alendronate for the treatment and prevention of osteoporosis and a motivation for that regimen (to "avoid dosing problems"); and that, as the district court found, it was "known" that once-weekly administration of alendronate would be effective for osteoporosis. (A59). Teva also demonstrated the exceptionally high level of ordinary skill in the art, which the parties do not dispute. (*Id.*). Finally, Teva showed that at most the only difference between the prior art and the claimed invention is the precise dosage strength – 80 mg vs. 70 mg and 40 mg vs. 35 mg – a difference that is not meaningful in light of the fact that a person skilled in the art would have chosen 70 mg weekly for treatment and 35 mg weekly for prevention – seven times the daily dose. (A643-44; A776-78). Based on those facts, which are not disputed, the district court should have found the claimed invention obvious.

A. The District Court Erred By Ignoring the Teachings of the *Lunar News*

1. The District Court Erred in Discarding the *Lunar News* Disclosures Based On the Credentials of Their Author

Neither the district court nor Merck cites any authority supporting the idea that prior art may be excluded from consideration because of the pedigree of the person who wrote it. The only relevant question is what a reference places in the public domain. Although Teva disputes Merck's mischaracterization of Dr. Mazess's knowledge and standing in the bone resorption and osteoporosis fields, his status is not relevant.⁵ Prior art references must be considered for all that they disclose and fairly suggest. *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983); *In re Oelrich*, 579 F.2d 86, 91, 198 USPQ 210, 214 (CCPA 1978); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). There is no exception to that rule based on where the author went to school.

⁵ Dr. Mazess directed the Bone Mineral Laboratory at the University of Wisconsin, he established bone densitometry as a viable diagnostic tool, founded the first manufacturer of bone densitometry measuring equipment, participated in and designed clinical trials in osteoporosis patients, and was widely published in the bone disease field. "Anthropologist" or not, he had vast experience in the area. (A4822-36; Blue Br. 11-12).

Nor is the absence of “peer review,” on which the district court also relied, an excuse to discredit the prior art. The *Lunar News* was a “printed publication,” which is all the statute requires. 35 U.S.C. § 102(a). Moreover, it was in the relevant field, and it was widely read by practitioners. Merck’s principal trial expert read it (A781), and its principal inventor had a copy of the July 1996 article in his possession. (A76-77). The disclosures in the April and July 1996 *Lunar News* are scientifically correct (A772-74) and exhaustively documented with the citation of 30 references. Merck dealt with its author on a business and professional basis. In fact, in May 1997, before Merck’s invention date, a Merck delegation, including a senior vice-president and Merck’s principal inventor, visited Dr. Mazess to discuss business arrangements between Merck and Lunar Corp., as well as articles that had appeared in the *Lunar News*. (A623-627; A670-74; A1308; A1309-29; A1330; A4765-68; A4885-88).

Finally, Merck’s patent application was likewise not “peer reviewed.” Neither the district court nor Merck attempted to justify Merck’s double standard – that a prior art publication must be peer reviewed to be effective against a patent application that is not.

2. The '329 Patent Discloses Nothing More than the *Lunar News*

Merck's attack on Dr. Mazess's credentials here is particularly inappropriate, since the '329 patent provides the public with nothing beyond what is disclosed in the *Lunar News*. Merck argues that the "failure of the *Lunar News* articles to address the known safety concerns or to discuss the side effect implications of high alendronate dosing for osteoporosis rendered their suggestions meaningless." (Red Br. 49). The district court apparently agreed with this argument. (A68). Even assuming that such safety concerns about weekly administration of alendronate existed in 1997, the '329 patent includes nothing more than does the *Lunar News* to dispel them, and by Merck's reasoning must also be "meaningless."

The '329 patent does not include data or reports of experimentation proving the workability of an idea that was contrary to some conventional wisdom. Merck's inventors had no such information. On the contrary, the patent provides nothing beyond what Dr. Mazess had already disclosed in the *Lunar News*. Specifically, the '329 patent includes no clinical trial data or results from studies in people proving the safety and effectiveness of the once-weekly administration of alendronate. (A642-43). Recognizing this weakness, Merck now feebly attempts to rely on the beagle experiments described in Example 1 in the '329 patent. (Red Br. 57). However, the

Merck scientist who conducted them testified that they were not relevant to patients taking alendronate (A4859; A4862), and Merck's trial expert testified that the dog experiments did not support the safety of once-weekly administration of alendronate and that they were not relevant to human experience. (A409).

Merck points out that human data are not required for patents on pharmaceutical inventions (Red Br. 57 n.7), but neither are such data required of a prior art reference to make it effective. Merck's '329 patent did not convey to the public anything not already disclosed in the April and July 1996 editions of the *Lunar News*, and Merck is not entitled to a patent for applying its name and employing its prestige to buttress Dr. Mazess's idea.

B. The District Court Erred By Failing Properly to Analyze the Obviousness Issue

The focus of the obviousness analysis is whether the claimed invention ("the subject matter to be patented") would have been obvious to a person of ordinary skill in the art in light of the differences between the prior art and what is claimed. *See Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 808, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989):

[T]he proper focus of an obviousness inquiry is on whether 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art.’

(See Blue Br. 38-39). The district court did not carry out this analysis.

The district court described the *Lunar News* and quoted the appropriate sections. Mentioning the prior art and quoting from it, however, is not enough. Merck asserts that the district court weighed the evidence in coming to its decision. (Red Br. 47-48). “Weighing the evidence” is no substitute for the appropriate section 103 analysis. Here, the district court never considered whether administering 70 mg and 35 mg once per week would have been obvious in view of a prior art disclosure of administering 80 mg and 40 mg once per week. Thus, although the district court discussed the *Lunar News*, in substance it failed to consider its teachings.

Merck does not dispute that the district court did not carry out the requisite analysis. Instead, it argues that Teva’s arguments are “fraught with hindsight.” (Red. Br. 48). The disclosures of the *Lunar News* are not hindsight. They are clear suggestions to administer alendronate once per week at a dose approximately seven times the daily dose. Whether many physicians would have accepted the suggestions at the time is irrelevant. Dr. Mazess was the first to believe in this concept, and he disclosed it publicly long before Merck’s inventors had the same idea. The public is entitled to practice freely what Dr. Mazess placed in its domain.

The implications of the district court's approach highlight its error. Under the district court's analysis, if rather than publish his idea in July 1996, Dr. Mazess had filed a patent application claiming it, when that patent issued it would not be effective prior art against the '329 patent because Dr. Mazess, the inventor, was an "anthropologist," his patent application was not "peer reviewed," and it "did not overcome the known side effects of alendronate. . . ." In fact, under the district court's analysis, if Dr. Mazess had filed a patent application claiming his concept, and if the Patent Office had declared an interference between his application and the application for the '329 patent, Dr. Mazess would have lost for the same reasons even though he was the prior inventor. No court has ever held, however, that the teachings of a prior art patent can be disregarded, nor has any interference been decided, based of the inventor's academic credentials or because the patent application was not peer reviewed before it was filed.

C. The Perception that Higher Weekly Doses of Alendronate Would Cause Increased Gastrointestinal Side Effects Did Not Exist

1. The District Court's Finding that Persons Skilled in the Art Would Have Been Afraid of Once-Weekly Alendronate is Clearly Erroneous

Merck spends most of its brief cobbling together the "facts" that it contends support the existence of a "dogma" in the art of osteoporosis

treatment in 1997 that “[i]n osteoporosis therapy, doses of alendronate higher than 20 mg were associated with an undesirable safety profile.” (Red. Br. 46). According to Merck, the inventors of the ’329 patent departed from conventional approaches “without any reasonable expectation of success.” (Red Br. 47). As discussed above, even if this were true, it would be irrelevant, because they did so a year too late – after Dr. Mazess had done the same thing and disclosed their invention to the public. In any event, it is not true.

In the end, Merck cannot escape the pre-litigation admissions of its inventors that the state of the art foretold success, not failure, with a once-weekly regimen. Merck first relies on several case reports of rare cases of esophageal erosion attributed to daily alendronate. (Red Br. 13-14). Merck falsely states that Teva had urged that the articles “should not have been considered.” (Red Br. 53-54). As explained in Teva’s opening brief, Merck, scientists at the time, and the experts at trial all attributed these cases to “pill esophagitis,” i.e., pills sticking in the patients’ esophagi, principally because those patients failed to follow Merck’s dosing instructions. (Blue Br. 52). In early 1996, after Merck promulgated its “Dear Doctor” letter emphasizing the need to follow those instructions, the problem disappeared. (Blue Br. 51).

Merck offered no evidence that those in the art actually held the view that a higher dose, administered only once per week, would cause an increased incidence of gastrointestinal side effects. Instead, Merck spins its story from a single study, the Chesnut report, which is the centerpiece of both Merck's case and the district court's opinion. As discussed in Teva's opening brief, the Chesnut study did not involve weekly administration of alendronate. It does not say that weekly dosing would be poorly tolerated or that no patient would be able to tolerate once-weekly doses of alendronate. (Blue Br. 53-55). Indeed, in the April 1996 issue of the *Lunar News* in which he disclosed once-weekly dosing of alendronate, Dr. Mazess cited the Chesnut study (A3066 ref. 4), and before this litigation provided a motive to take the opposite view, Merck also cited Chesnut in support of the idea of weekly dosing. (*See, e.g.*, A1726). The district court's finding that the paper supported "clearly documented and known dose related gastrointestinal side effects" that would have deterred once-weekly dosing of alendronate is clearly erroneous.⁶

⁶ Merck also cites a Teva patent as confirming a "perception" in the art. (Red Br. 12). This patent is directed to a particular formulation for sustained release, and Merck deliberately omits the crucial fact that the passage it cites refers specifically to "sustained release doses." (A4414, col. 3, lines 38-39). Sustained release formulations and the problems associated with them have nothing to do with the issues here.

Recognizing the lack of support for its contention that there was an expectation of “dose-related” side effects with alendronate, Merck turns to evidence regarding experiences with other drugs — pamidronate, clodronate and etidronate — in an attempt to demonstrate that side effects were known to be “dose-related.” (Red Br. 8-9). However, as the district court found, because of variability among these compounds, “results obtained with one bisphosphonate cannot be extrapolated readily to the whole class,” and evidence regarding the use of etidronate, clodronate and pamidronate “holds little weight . . . given the unique characteristics of each bisphosphonate.” (A60-61).

In the end, Merck’s spin on the evidence is impeached by its own pre-litigation documents, most of which were authored by its inventors. Merck characterizes these documents as reflecting “the inventors’ own rationales to overcome the skepticism about the use of high unit doses.” (Red Br. 57). Merck, however, cannot escape these admissions. As discussed in Teva’s opening brief, before this litigation, Merck’s inventors presented evidence to Merck management, the FDA and the scientific community that once-weekly dosing would be “well tolerated,” that it would be “unlikely to have a greater potential to induce upper GI irritation,” and that weekly dosing should be “very well-tolerated.” (Blue Br. 55-60). The inventors cited

Chesnut in coming to these conclusions, thus undermining Merck's argument that it provided a significant deterrent to the idea of once-weekly dosing.

In concluding that once-weekly dosing was likely to be well-tolerated, Merck's inventors also relied on data from studies in Paget's patients. Merck attempts to elide this point by arguing that in each of the documents the inventors "consistently rely on the animal studies." (Red Br. 57). However, even cursory review of the documents demonstrates that the inventors relied on the Paget's disease data to demonstrate the expected side effect profile of once-weekly dosing in osteoporosis. In a March 1998 submission to the FDA, Merck stated:

Experience in Paget's patients (up to 80 mg alendronate for 6 months) suggests that dosing regimens of either 35 or 70 mg weekly, and 35 mg twice-weekly should be well-tolerated.

(A1711-14; A1735).

The district court concluded that data from Paget's studies were not relevant because "it was well-known to those of ordinary skill in the art that patients with Paget's disease tolerate higher doses of alendronate than patients with osteoporosis." (A65 n.8). As demonstrated above, and in Teva's opening brief, neither Merck nor its inventors held this view before this litigation. They never told the FDA or Merck management or the

scientific community that gastrointestinal data from Paget's patients could not be extrapolated to osteoporosis patients because of tolerability differences between the patient populations. To the contrary, Merck and its inventors extrapolated repeatedly from the Paget's data in drawing conclusions about the likely tolerability of higher doses of alendronate in osteoporosis patients. The district court's decision to set aside the data from Paget's patients was clearly erroneous.

2. Merck's Attacks On Dr. Russell Are Baseless

In support of its "fear defense," Merck repeatedly criticizes Dr. Russell. According to Merck, that Dr. Russell did not make the patented invention himself is evidence of its unobviousness and impeaches Dr. Russell's testimony. Specifically, Merck asserts that if the invention was obvious, Dr. Russell would have instructed his consulting client, Procter & Gamble, to make a once-weekly version of its drug, risedronate.

Merck's argument is specious. Nothing in the record bears on whether an alternative dosing regimen for risedronate would or would not have been obvious. The record contains no evidence about its mode of action, effectiveness, bioavailability over time or the scope and content of the prior art with respect to it. In fact, the July 1996 *Lunar News*, the most relevant prior art reference with respect to weekly alendronate, does not

mention risedronate. Thus, whether weekly risedronate dosing would have been obvious or unobvious is, as far as this record is concerned, unknown and irrelevant to the issues here.⁷

Similarly, Merck refers to statements by Dr. Russell about bisphosphonates other than alendronate that allegedly support Merck's position that gastrointestinal side effects were expected to be dose-related. Like all of the evidence regarding the other bisphosphonates, this evidence is irrelevant to expectations with alendronate. (A60-61).

Finally, Merck falsely characterizes a 2002 declaration Dr. Russell submitted in a Canadian lawsuit. Merck selectively quotes from the document, arguing that with respect to side effects, Dr. Russell refused to extrapolate from Paget's disease to osteoporosis. First, Dr. Russell's declaration concerned etidronate not alendronate, and thus is not relevant to the issues in this case. Moreover, at trial Dr. Russell explained that the side effect under consideration was not a gastrointestinal issue, but instead the bone mineralization problem associated uniquely with etidronate, and that the issue was whether one could extrapolate doses from one population to

⁷ In any event, whether Dr. Russell made the invention is irrelevant. *Amazon.com, Inc. v. Barnes & Noble.com, Inc.*, 239 F.3d 1343, 1364, 57 USPQ2d 1747, 1762 (Fed. Cir. 2001) ("Whatever [the expert] did or did not personally realize at the time . . . is irrelevant").

the other in terms of that side effect. (A467-71). Merck's characterizations of Dr. Russell are false, and do not support Merck's contention that the claimed invention would not have been obvious.

D. The Commercial Success of Once-Weekly Alendronate Does Not Demonstrate Nonobviousness

Merck includes statistics showing that alendronate is a big seller, and that alendronate sales continued to rise after the weekly version replaced the daily dose. Whether weekly alendronate is successful is not an issue. The issue instead is whether that success proves anything about the nonobviousness of the claimed invention.

Quotations from court decisions about the probative nature of commercial success (Red Br. 59-60) are not pertinent when they are taken from their contexts, as Merck has done. Merck does not dispute the rationale for the consideration of commercial success: when present it may show that the solution the inventor devised was not obvious to persons skilled in the art because they had the incentive to fulfill a market demand and could not do so. (Blue Br. 61-62). Nor does Merck dispute the converse of that principle: that if barriers to entry unrelated to the patented invention precluded others from participating in the market, the patentee's success cannot be probative of unobviousness. Merck concedes the existence of such barriers here.

Specifically, from 1988, when it acquired the '077 patent, until 2007, when that patent expires, Merck has a legal exclusivity over the administration of alendronate at any dose, and during the relevant period here, 1995 through 2000, it also had a "new chemical entity" exclusivity, independent of patent rights. *See* 21 U.S.C. § 355(c)(3)(D)(ii). Thus, at all relevant times Merck had sole control over the marketplace. Every potential competitor knew that even if it developed a new alendronate product, it would be unable to sell it. It defies common sense to believe that under those circumstances, a competitor would even consider making the enormous investment required to bring a new drug product to market, whether or not it was obvious to do so.

The commercial success of weekly alendronate shows that it was a good idea – precisely as the *Lunar News* had taught. Good ideas are patentable only if they are not obvious, and Merck's success says nothing about whether that idea would have been obvious.

Recognizing the problem it faces, Merck cites to other drugs, such as risedronate, marketed by Proctor & Gamble. (Red Br. 60). Merck does not explain what risedronate has to do with this case. Again, the record contains no evidence about whether weekly administration of risedronate would have

been obvious, or what the prior art landscape with respect to risedronate was.

Merck's reliance on Teva's own sustained release formulation patent is likewise misplaced. (Red Br. 60-61). That patent was not even filed for until long after both the *Lunar News* was published and '329 patent had issued. The record contains no evidence of what Teva was doing in 1996, or whether Teva had any "incentive" to make weekly dosage forms of alendronate in 1996, particularly when that drug was subject to at least a five-year FDA exclusivity.

Finally, the fact that Teva seeks approval to market a generic version of Merck's drug does not mean that the dosage regimen would not have been obvious, only that it is a valuable product for the reasons expressed in the *Lunar News* – it "avoids dosing problems." Teva seeks only to do what is taught by the *Lunar News*: market alendronate for osteoporosis treatment and prevention.

CONCLUSION

For the foregoing reasons and for the reasons set forth in Teva's principal brief, the district court's judgment should be reversed.

Respectfully submitted,

April 15, 2004

A handwritten signature in cursive script, appearing to read "James Galbraith", written over a horizontal line.

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CERTIFICATE OF SERVICE

I hereby certify that on this date I served the foregoing Reply Brief of Defendant-Appellant Teva Pharmaceuticals USA, Inc. on plaintiff-appellee Merck & Co., Inc. by causing two copies thereof to be delivered by overnight courier to

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counsel for Merck & Co.

April 15, 2004


A handwritten signature in cursive script, appearing to read "James Galbraith", is written over a horizontal line.

James Galbraith

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of F.R.A.P. 32(a)(7)(c). This brief contains 6640 words.

April 15, 2004



James Galbraith

EXHIBIT I

determined that the MOU was an enforceable agreement and that it would not be necessary to resume a full trial on the merits of the case, there were only limited avenues to establish a basis for appeal, namely, by interlocutory or final judgment.

Genesis could have sought permission under 28 U.S.C. § 1292(b) and (c)(1) to immediately appeal the interlocutory judgment and order of the district court, or Genesis could have made the required payment pursuant to the MOU with the appropriate certification of receipt by Silicon. None of these avenues was followed, therefore there is no interlocutory or final judgment from which an appeal can be taken. Since under 28 U.S.C. § 1295(a)(1) this Court cannot review a decision by a district court that is not final, we dismiss this case for lack of jurisdiction.

DISMISSED

COSTS

No costs.



**MERCK & CO., INC., Plaintiff–
Appellee,**

v.

**TEVA PHARMACEUTICALS USA,
INC., Defendant–Appellant.**

No. 04–1005.

United States Court of Appeals,
Federal Circuit.

DECIDED: Jan. 28, 2005.

Background: Owner of patent for osteoporosis drug sued proposed manufacturer of generic version for infringement. The United States District Court for the District of Delaware, Joseph J. Farnan, Jr., J., 288 F.Supp.2d 601, held for owner, and competitor appealed.

Holdings: The Court of Appeals, Gajarsa, Circuit Judge, held that:

- (1) “about” 70/35 mg of alendronate monosodium trihydrate, called for in patent claims, meant approximately those amounts, and
- (2) patent was invalid as obvious.

Reversed.

Rader, Circuit Judge, dissented and filed opinion.

1. Federal Courts ⇨776, 850.1

On appeal from a bench trial, appellate court reviews district court’s conclusions of law de novo and its findings of fact for clear error.

2. Federal Courts ⇨853

District court’s factual finding is “clearly erroneous” when, despite some supporting evidence, reviewing court on entire evidence is left with definite and firm conviction that mistake has been committed.

See publication Words and Phrases for other judicial constructions and definitions.

3. Patents ⇨324.5

Patent claim construction is question of law, reviewed de novo.

4. Patents ⇨324.5, 324.55(4)

Patent obviousness is question of law, reviewed de novo, based on underlying factual determinations, which are reviewed for clear error. 35 U.S.C.A. § 103.

5. Patents ⇨16(2, 3), 16.13, 36.1(1)

Factual determinations underlying finding of patent invalidity on ground of obviousness include (1) scope and content of prior art, (2) level of ordinary skill in the art, (3) differences between claimed invention and prior art, and (4) objective indicia of nonobviousness. 35 U.S.C.A. § 103.

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6. Patents ⇨101(2)

“About” 70/35 mg of alendronate monosodium trihydrate, called for in claims of patent for osteoporosis drug, meant approximately those amounts; statement in specification which could have been taken as requiring exactly amount called for was insufficiently clear to warrant abandonment of term’s ordinary meaning.

7. Patents ⇨165(3)

To properly construe patent claim term, court first considers intrinsic evidence, starting with language of claim.

8. Patents ⇨161

Generally, patent claim terms should be construed consistently with their ordinary and customary meanings, as determined by those of ordinary skill in the art.

9. Patents ⇨162, 167(1)

Patent-construing court must examine specification to determine whether patentee acted as his or her own lexicographer of term that otherwise has ordinary meaning to person of skill in the art.

10. Patents ⇨162, 167(1.1)

When patentee acts as his or her own lexicographer in redefining meaning of particular claim terms away from their ordinary meaning, he or she must clearly express that intent in specification; statement in specification must have sufficient clarity to put one reasonably skilled in art on notice that inventor intended to redefine claim term.

11. Patents ⇨157(1)

Patent claim construction that gives meaning to all terms of claim is preferred over one that does not do so.

12. Patents ⇨16.25

Patent for osteoporosis drug, calling for once-weekly dosage at seven times daily dose in order to overcome dose-related side effect, was invalid as obvious in light of widely-circulated prior art articles by industry expert calling for same strategy

to overcome same side effect, even though articles were not published in peer-reviewed journal and author did not possess professional credentials. 35 U.S.C.A. § 103.

13. Patents ⇨36.2(9)

Commercial success of patented osteoporosis drug did not weigh against finding of patent invalidity on ground of obviousness where author of allegedly invalidating prior art articles was not in position to commercially exploit idea. 35 U.S.C.A. § 103.

Patents ⇨328(2)

4,621,077. Cited.

Patents ⇨328(2)

5,994,329. Invalid and Not Infringed.

John F. Lynch, Howrey Simon Arnold & White, LLP, of Houston, Texas, argued for plaintiff-appellee. With him on the brief were Nicolas G. Barzoukas and Richard L. Stanley. Of counsel on the brief were Paul D. Matukaitis, Edward W. Murray and Gerard M. Devlin, Merck & Co., Inc., of Rahway, New Jersey.

James Galbraith, Kenyon & Kenyon, of New York, New York, argued for defendant-appellant. With him on the brief were Maria Luisa Palmese and William G. James, II.

Before RADER, GAJARSA, and PROST, Circuit Judges.

GAJARSA, Circuit Judge.

Teva Pharmaceuticals USA, Inc. (“Teva”) appeals the final judgment of the United States District Court of Delaware, which, after a bench trial, found Merck & Co.’s (“Merck”) U.S. Patent No. 5,994,329 (issued Nov. 30, 1999) (“the ’329 patent”)

not invalid as anticipated or obvious. The district court further found the '329 patent to be enforceable, and the '329 patent claims 23 and 37 constructively infringed by Teva's Abbreviated New Drug Application ("ANDA") under 35 U.S.C. § 271(e)(2)(A) of the Hatch-Waxman Act. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 288 F.Supp.2d 601 (D.Del.2003) ("*Merck*"); *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, No. 01-CV-0048, Order (D.Del. Sept. 24, 2003) (Final Judgment Order Pursuant to Fed.R.Civ.P. 54(b)) ("*Final Judgment Order*").¹

We disagree with the district court's construction of the claim term "about" in claims 23 and 37 of the '329 patent. Because we further hold claims 23 and 37 obvious in light of the prior art, we vacate the judgment of the district court and hold the claims invalid and not infringed.

I. BACKGROUND

A. '329 Patent

Merck owns the '329 patent. The '329 patent, entitled "Method for Inhibiting Bone Resorption," teaches a method of treating and preventing osteoporosis through less-than-daily administration of bisphosphonate compounds. '329 patent, col. 1, ll. 15–25. The patent was filed on August 14, 1998, and Merck stipulated at trial that it would not allege an invention date prior to July 22, 1997 for the claims at issue. *Merck*, 288 F.Supp.2d at 606.

Bisphosphonates are a family of chemical compounds that are known to selectively inhibit the bone destruction process that contributes to osteoporosis and other bone diseases. '329 patent, col. 1, ll. 45–50. Bisphosphonates include, among other compounds, alendronate, risedronate, tiludronate, pamidronate, ibandronate, zolendronate, and etidronate. *Id.* at col. 1, ll.

54–65; col. 2, ll. 28–31. At issue in this case are once-weekly dosages of alendronate monosodium trihydrate.

Bisphosphonates are not readily absorbed by the gastrointestinal ("GI") tract. The medications thus require rigorous dosing instructions: a patient must take the medicine on an empty stomach and remain upright and fasting for thirty minutes after ingestion. '329 patent, col. 2, ll. 3–24. In addition, the compounds are known to have adverse GI side effects that physicians believed to be related, in part, to (a) irritation to the patient's esophagus, or (b) the size of the dose. *Id.* at col. 2, ll. 23–46.

Before the '329 patent issued, standard osteoporosis treatments consisted of small daily doses of bisphosphonates to avoid GI complications. *Id.* at col. 1, ll. 54–61; col. 2, ll. 34–35, 44–46. According to the patent, however, the adverse GI side-effects resulting from repetitive irritation to the GI tract were the primary concern in the field. *Id.* at col. 2, ll. 65–67; col. 3, l. 57—col. 4, l. 13. The inventors trumpeted the reduced-frequency dosing schedule disclosed in the '329 patent as decreasing the irritating effect of the compounds, as well as increasing patient compliance with the rigorous dosing instructions. *Id.* at col. 3, ll. 57–64; col. 4, ll. 14–23.

This case involves dependent claims 23 and 37 of the '329 patent. At trial, the parties agreed to cast the text of these claims in independent form, incorporating all the dependent limitations:

23. A method for *treating* osteoporosis in human comprising orally administering *about 70 mg* of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

1. On appeal, Teva does not challenge the district court's determination that the '329 pat-

ent is enforceable or that it would be infringed by Teva's proposed drug product.

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37. A method *for preventing* osteoporosis in human comprising orally administering *about 35 mg* of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.

'329 patent, col. 21, ll. 24–27 (claim 23) (emphasis added); col. 22, ll. 24–26 (claim 37) (emphasis added). We note that the only differences between claim 23 and claim 37 are (1) the dosage amount of alendronate monosodium trihydrate (70 mg or 35 mg) and (2) whether the method is directed to treating or preventing osteoporosis.

Merck has Food and Drug Administration ("FDA") approval to market both a once-weekly and a relatively diminished daily dose of alendronate monosodium trihydrate, which it does under the trade name Fosamax. *Merck*, 288 F.Supp.2d at 605.

B. Litigation

In late 2000, Teva amended an existing ANDA and sought FDA approval to mar-

ket generic versions of Merck's once-weekly Fosamax supplement in 35 mg and 70 mg quantities.² *Merck*, 288 F.Supp.2d at 605–06; Teva Br. at 4. Merck subsequently filed suit against Teva under 35 U.S.C. § 271(e)(2)(A), alleging Teva's ANDA filing was an act of infringement.³

According to the trial court, Merck acted as its own lexicographer and through the specification redefined the ordinary meaning of "about" in claims 23 and 37—which both parties agree has the ordinary meaning "approximately"—to something quite different. *Merck*, 288 F.Supp.2d at 612–16. Thus, the district court concluded the terms "about 35 mg" in claim 37 and "about 70 mg" in claim 23 mean *exactly* 35 (or 70) mg of alendronic acid.⁴

Relying on this construction of "about," the district court dismissed Teva's allegations that the claims at issue were (1) anticipated by a July 1996 *Lunar News* article or (2) rendered obvious by an April 1996 *Lunar News* article combined with the July 1996 article.⁵ The trial court found both articles qualified as prior art publications under 35 U.S.C. § 102(a). *Merck*, 288 F.Supp.2d at 618–19. The

2. Teva filed one amendment for the once-weekly 70 mg dosage, and later filed another for the once-weekly 35 mg dosage. *Merck*, 288 F.Supp.2d at 605–06. Merck separately sued Teva for infringement, under 35 U.S.C. § 271(e)(2)(A), based on each ANDA amendment. *Id.* The district court consolidated those suits in the present action.

3. The present case relates to another action between the two parties involving Merck's daily formulation of Fosamax. The district court found Teva's proposed generic daily alendronate compound would infringe Merck's patent on that drug, and this court affirmed that decision. *Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367 (Fed.Cir.2003). In this action the parties agreed to be bound by the judgment from this court on issues relating to the daily formulation. As a result, the only issues before the district court in this case related to the '329 patent. *Merck*, 288 F.Supp.2d at 606.

4. That is, the trial court construed "the disputed claim terms 'about 70/35 mg' to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories." *Merck*, 288 F.Supp.2d at 616.

5. *Lunar News* is a quarterly newsletter distributed to approximately 15,000 to 20,000 physicians and others in the medical art by Lunar Corporation, a manufacturer of bone densitometry equipment used to diagnose osteoporosis. *Merck*, 288 F.Supp.2d at 618–19; Teva Br. at 11–12. The author of each article is Dr. Mazess, who has a doctorate degree in anthropology, but does not have formal training in pharmacology. *Id.* Teva points out, however, that Dr. Mazess directed the Bone Mineral Laboratory at the University of Wisconsin, established bone densitometry as a diagnostic tool, founded the first manufacturer of bone densitometry measuring equipment (Lunar), was Lunar's first president, has participated in and designed clinical trials for

April 1996 article in *Lunar News* recommends weekly dosages of alendronate to improve patient compliance:

[O]ne of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is bioavailable. Even coffee or juice reduces this by 60%, and a meal reduces it by >85%. Alendronate must be taken, after an overnight fast, 30–60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly [to] maintain chronically. *An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested.*

Update: Bisphosphonate, Lunar News, Apr. 1996, at 31 (emphasis added).

The July 1996 *Lunar News* article further emphasizes the need for a once-weekly dose of Fosamax because “[s]ome United States physicians are reluctant to treat [patients with Fosamax] because of: a) side effects; b) difficulty of dosing; and c) high costs (\$700/year).” The author suggests:

The difficulties with oral bisphosphonates may favor their episodic (*once/week*) or cyclical (one week each month) administration. Even oral alendronate potentially could be given in a *40 or 80 mg dose once/week* to avoid dosing problems and reduce costs.⁶

osteoporosis treatment, and is widely published in the bone disease field.

6. Teva argues that the 40 mg and 80 mg amounts were recommended because 40 mg tablets of alendronate monosodium trihydrate were commercially available for those who suffer from Paget’s disease, a bone disorder that also responds to bisphosphonate treatment. The standard daily dose of Fosamax is

Update: Bisphosphonate, Lunar News, July 1996, at 23 (emphasis added).

Regarding anticipation, the trial court held the July 1996 article does not “expressly or inherently disclose the dosage amounts for alendronate in claims 23 and 37” because there was no evidence that 40 mg and 80 mg of alendronate contains “the same number of alendronate core molecules” as found in 35 mg and 70 mg, respectively, of alendronic acid. *Merck*, 288 F.Supp.2d at 618–20.

As for obviousness, the district court concluded the suggestion of weekly treatment was not “clinically useful or obvious in July 1997 because of the known dose-related gastrointestinal side effects” associated with the daily formulation of Fosamax. *Merck*, 288 F.Supp.2d at 628. Although it is undisputed that a once-weekly dosage was known to be efficacious, the court determined that the *Lunar News* articles could not overcome doctors’ concerns associated with higher dosages because the *Lunar News* articles were not published in peer-reviewed journals or authored by one skilled in the art. *Merck*, 288 F.Supp.2d at 628–29.

Finding the ’329 patent not invalid as anticipated or obvious, the district court delayed the effective date of the FDA approval of Teva’s ANDA until the ’329 patent expires and enjoined commercial sale of Teva’s generic treatment. *Final Judgment Order* at 1. This appeal followed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

5 mg or 10 mg. Exact multiples of the standard daily dose corresponding to the amount of Fosamax administered in a week, i.e., 35 mg or 70 mg, were not commercially available at the time of the 1996 *Lunar News* articles. Thus, Teva argues, the 40 mg and 80 mg dosages should be viewed as teaching the ’329 patent’s seven-fold increase in daily dosages (5 and 10 mg), in terms of the 40 mg doses then-available on the market.

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II. DISCUSSION

A. *Standard of Review*

[1,2] On appeal from a bench trial, this court reviews the district court's conclusions of law *de novo* and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed.Cir.2004); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1123 (Fed.Cir.2000). A finding is clearly erroneous when, despite some supporting evidence, "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. United States Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 92 L.Ed. 746 (1948).

[3–5] The court reviews claim construction, a question of law, *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed.Cir.1998) (en banc). Obviousness is a question of law based on underlying factual determinations. *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). The court reviews an obviousness ruling *de novo*, but reviews the underlying factual findings for clear error. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966); *Golden Blount*, 365 F.3d at 1058. The underlying factual determinations include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobviousness. *Graham*, 383 U.S. at 17–18, 86 S.Ct. 684.

B. *Claim Construction*

In finding that Merck acted as its own lexicographer, the district court relied on the following passage from the specification:

7. The dissent frames the dispute in terms of the entire phrase "about 70[35] mg of alen-

Because of the mixed nomenclature currently in use by those or [sic] ordinary skill in the art, reference to a specific weight or percentage of bisphosphonate compound in the present invention is on an active weight basis unless otherwise indicated herein. *For example the phrase "about 70 mg of bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof and mixtures thereof, on an alendronic acid weight basis" means that the amount of bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.*

'329 patent, col. 10, l. 65—col. 11, l. 8 (emphasis added). According to the district court's opinion, the patentee uses the phrase "about 35 [or 70] mg" to account for variations in the molecular weight of the different derivatives of alendronic acid and to deliver *exactly* 35 (or 70) mg of alendronic acid. *Merck*, 288 F.Supp.2d at 613. For example, the court noted that alendronate monosodium trihydrate, which is used in Fosamax, requires an atom of sodium for each molecule. *Id.* at 613–14. If a heavier metal were chosen, such as potassium, the weight of the derivative compound would have to increase to deliver exactly the same number of molecules of the active alendronate compound found in 35 [or 70] mg of alendronic acid. *Id.* at 614. The district court thus construed the term "about 35 [or 70] mg" to mean the amount of the derivative compound that gives *exactly* 35 [or 70] mg of the active compound.

[6–9] We reverse the district court's construction of "about" and hold that such term should be given its ordinary meaning of "approximately."⁷ To properly con-

dronate monosodium trihydrate, on an alendronic acid basis." Post at 2:22–3:2. Not-

strue a claim term, a court first considers the intrinsic evidence, starting with the language of the claims. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996). Generally claim terms should be construed consistently with their ordinary and customary meanings, as determined by those of ordinary skill in the art. *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir.2003). While in some cases there is a presumption that favors the ordinary meaning of a term, *Tex. Digital Sys. v. Telegenix Inc.*, 308 F.3d 1193, 1202 (Fed. Cir.2002), the court must first examine the specification to determine whether the patentee acted as his own lexicographer of a term that already has an ordinary meaning to a person of skill in the art. *See, e.g., Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed.Cir.1998); *Brookhill-Wilk*, 334 F.3d at 1299.

[10] When a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description. *See, e.g., Bell Atl. Network Servs. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed.Cir.2001). We have re-

withstanding this contention, the district court identified the "disputed claim terms" as "about 70 / 35 mg." *Merck*, 288 F.Supp.2d at 616. In its brief to this court, Merck likewise stated the issue as whether the district court properly construed the aforementioned limitation (not disputed term) on grounds that the '329 patent expressly defined "about 70 mg" as calculated "based on 70 mg of alendronic acid." *See* Appellee Br. at 3 (statement of issues). We agree with Merck, and the district court, that the dispute concerns the proper meaning of "about." We thus understand the dissent to argue that meaning is fixed by the context of the claim and the language of the written description.

It is correct to look first to those sources for the meaning at issue. *See Vitronics*, 90 F.3d at 1582. However, as is noted above when

peatedly emphasized that the statement in the specification must have sufficient clarity to put one reasonably skilled in the art on notice that the inventor intended to redefine the claim term. *Id.*; *see also Elekta Instrument S.A. v. O.U.R. Sci. Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed.Cir. 2000) ("Absent an express intent to impart a novel meaning, claim terms take on their ordinary meaning."); *Renishaw*, 158 F.3d at 1249 ("The patentee's lexicography must, of course, appear 'with reasonable clarity, deliberateness, and precision' before it can affect the claim.") (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed.Cir. 1994)); *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, 1177-78 (Fed.Cir.2002) (stating that the "presumption in favor of the claim term's ordinary meaning is overcome, however, if a different meaning is clearly and deliberately set forth in the intrinsic evidence"). In the present case, the passage cited by the district court from the specification for Merck's definition of "about" is ambiguous. It fails to redefine "about" to mean "exactly" in clear enough terms to justify such a counterintuitive definition of "about."

The phrase's ambiguity arises from the fact that it can easily be read as Teva

the intrinsic evidence does not clearly establish its own lexicography, it is proper to determine the ordinary meaning of the term. For that reason we ascribe "about" its ordinary meaning here.

Moreover, the dissent pursues a philosophical argument as to the deference which should be given to the trial court. Claim construction being a legal matter it is reviewed *de novo* and this is still the law notwithstanding the desire of some members of this court to consider creating an exception to that rule. *See Cybor*, 138 F.3d at 1462-63 (Plager, J., concurring); *id.* at 1463-66 (Mayer, C.J., concurring in judgment); *id.* at 1473-75 (Rader, J., dissenting). Therefore, if we apply proper legal precedent as the majority has done in this case, the result is clear and obvious.

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does—as a way of explaining what is meant by the use of the phrase “alendronate acid active basis” rather than as a way of radically redefining what is meant by “about.” The district court construed the phrase “about 70 [or 35] mg” to mean that one should administer approximately 70 (or 35) mg of the *derivative compound*, such that the end result is that the patient is administered exactly 70 (or 35) mg of alendronic acid. In other words, the district court determined that the quantity specified in the claims (35 or 70 mg) modifies the amount of the *derivative compound* rather than the *active compound*. Under such a construction, the term “about” informs one of ordinary skill in the art to select whatever quantity of the derivative compound necessary to give exactly 35 (or 70) mg of alendronic acid; for alendronate monosodium trihydrate, the word “about” thus meant that 45.68 mg (or 91.35 mg) of that compound should be delivered—the amount necessary to give exactly 35 (or 70) mg of alendronic acid.

Unlike the limiting definition of “about” adopted by the district court, Teva’s interpretation of the paragraph in question would mean that “70 [or 35] mg” refers to the amount of the *active compound* to be administered rather than the amount of the derivative compound. The term “about” in the claims would then serve to modify the quantity of the *active compound* in a way consistent with its normal definition of “approximately.” Under this construction, the modifying phrase “about 70 [or 35] mg” would refer to approximately 70 (or 35) mg of *alendronic acid*.⁸

The claim construction urged by Merck and adopted by the district court reads the

sentence of the passage underlined above out of context. In the sentence before the highlighted sentence, the patentee informs those of ordinary skill in the art that, when the patent refers to a certain amount of a bisphosphonate compound, it is actually instructing them to administer a certain amount of the active component of the compound rather than the compound itself, i.e., that one should calculate the amount dispensed on an “active weight basis.” This preceding sentence thus acts to specify a common denominator to be used for all derivatives of alendronic acid. The underlined sentence merely gives a specific example—that of an alendronate derivative—to show what is meant by using the phrase “active weight basis.”

Given that the passage that Merck relies on is amenable to a second (and more reasonable) interpretation, we hold Merck did not clearly set out its own definition of “about” with “reasonable clarity, deliberateness, and precision,” and thus failed to act as its own lexicographer. *In re Paulsen*, 30 F.3d at 1480.

As further support for this conclusion, we note that other parts of the specification also suggest that “about” should be given its ordinary meaning of “approximately.” The specification repeatedly describes a range of acceptable dosage amounts, with the patentee emphasizing that unit dosages will vary. For example, the specification suggests that a once-weekly dosage amount could contain anywhere from *about* 17.5 mg to *about* 70 mg of any alendronate compound on an alendronate acid active basis, with *about* 35 mg and *about* 70 mg being only two examples of a unit dosage:

8. Merck argues that the district court’s construction is supported by the fact that “about” was not used twice in the underlined sentence cited by Merck, i.e., that the specification does not state that “the amount of bisphosphonate compound selected is cal-

culated based on *about* 70 mg of alendronic acid.” (emphasis added). While Merck’s grammatical savvy is noted, we believe that the omission of a second “about” is likely an inadvertent error rather than the product of meticulous drafting.

For once-weekly dosing, an oral unit dosage comprises from *about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis*. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

'329 patent, col. 12, ll. 56–63 (emphasis added). In addition to the above passage, at another point in the specification the range for the normal unit dosage is further widened to “about 8.75 to about 140 mg.” '329 patent, col. 12, ll. 52–55 (stating that “a unit dosage typically comprises from about 8.75 mg to about 140 mg of an alendronate compound on an alendronic acid active weight basis”). The specification thus suggests the patentee contemplated a range of dosages, further compromising Merck's proposition that it acted as its own lexicographer in defining “about” to mean “exactly.”⁹

[11] Finally, our construction of “about” eliminates the problem pointed out by Teva that the district court's construction of the term “about” renders other parts of the claim superfluous. As Teva notes, the specification uses both the term “about” and “on an alendronic acid basis” at least 15 times to describe a dosage strength. If, as Merck urges, “about 35 [or 70] mg” means exactly 35 (or 70) mg of alendronic acid, then the oft-repeated phrase “on an alendronic acid active basis” would be unnecessary since such an understanding would be clear simply by using the term “about.” A claim construction that gives meaning to all the terms of the

claim is preferred over one that does not do so. *Elekta*, 214 F.3d at 1307 (construing claim to avoid rendering the 30 degree claim limitation superfluous); *Gen. Am. Transp. Corp. v. Cryo-Trans, Inc.*, 93 F.3d 766, 770 (Fed.Cir.1996) (rejecting the district court's claim construction because it rendered superfluous the claim requirement for openings adjacent to the end walls). By construing “about” to mean its accepted and ordinary meaning of “approximately,” the phrase “alendronic acid basis” is no longer excess verbiage, but is instead necessary because it is the noun that “about 35 [or 70] mg” modifies.

Because the patentee did not clearly redefine “about” in the specification, and because the district court construed the claim term in a manner inconsistent with the specification, we reverse the district court's claim construction. We thus hold that the term “about” should be given its ordinary and accepted meaning of “approximately.”

C. Invalidity

In light of the corrected claim construction we find reversible error in the district court's obviousness analysis. A patent claim is invalid “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a) (2000). The ultimate issue of obviousness turns on four factual determinations: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4)

9. We also note that Examples 7 and 8 in the '329 patent do not contradict the construction we adopt on appeal because they are only examples of the tablets that could be

prepared according to the patent. Neither example clearly states that the only embodiment of the claims would be the exact formulations described therein.

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objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). As explained below, we find clear error in the trial court’s findings on these underlying facts.¹⁰ On reviewing these factual bases, we conclude the district court also erred in refusing to invalidate claims 23 and 37 for obviousness in view of the 1996 *Lunar News* articles.

[12] The central issue concerns the differences between the aspects of the invention claimed at claims 23 and 37, and the teachings of the *Lunar News* articles. As the district court necessarily recognized, there are more similarities than differences. These claims, and the July 1996 article, both teach administering alendronate once a week instead of once a day. These claims read in light of the specification, and the July 1996 article, both indicate—and it has been conceded as known in the art at the time¹¹—that for treating or preventing osteoporosis a once-weekly dosage at seven times the daily dose would be as effective as seven daily doses. The ’329 patent, and both the April and July 1996 articles, explain the motivation for a once-weekly dose as increasing patient compliance, by making it easier to take the drug (and incur the inconvenience of the rigorous dosing regimen less frequently). Although the claims teach 70 or 35 mg doses rather than the 80 or 40 mg doses disclosed in the July 1996 article, Dr. Arthur C. Santora—one of the co-inventors on the ’329 patent—admitted against Merck’s interest that a once-weekly 40 mg dose would be as effective as seven daily 5 mg doses, and a once-weekly 80 mg dose would be as effective as seven daily 10 mg doses, in preventing or treating osteoporosis. There was no great leap required of

those skilled in the art to go from 40 or 80 mg once a week, the pills available at the time to treat patients with Paget’s disease, to a 35 or 70 mg pill once a week. The district court’s conclusion that the claims are not obvious cannot rest on any of these similarities between the claimed invention and the two *Lunar News* articles.

The district court distinguished the two *Lunar News* articles on grounds that they failed to explain how the once-weekly dosing overcame concerns in the art with adverse GI side effects. *Merck*, 288 F.Supp.2d at 628–29. We are left with the firm conviction that this distinction is misplaced. As noted, the district court found those in the art had identified two types of adverse GI problems with alendronate. The first, and most significant, involved esophageal injury or repetitive irritation of the esophagus. The district court, reviewing the October 1996 article by DeGroen in the *New England Journal of Medicine*, expressly recognized the literature taught that complications related to alendronate were due to “prolonged contact of the drug with the esophagus.” *Merck*, 288 F.Supp.2d at 627. Confronted with this problem, Merck revised its dosing instructions and sent the clarifying materials to prescribing physicians in a March 1996 “Dear Doctor” letter. After Merck sent this letter, the reported incidence of GI distress fell to almost nothing even as the number of patients being prescribed Fosamax doubled by October 1996. Although the ’329 patent focuses on this adverse GI side-effect, it provides no additional motivation to overcome this problem beyond the motivation described in the two articles. The ’329 patent, both articles, and the prevailing knowledge of those skilled

10. It makes no difference to this conclusion whether the court begins with the claim construction set forth by the panel or the dissent. In either case, the district court erred in find-

ing the ’329 patent was not invalid as obvious in view of the *Lunar News* articles.

11. See *Merck*, 288 F.Supp.2d at 624.

in the art, recognized that to the extent “dosing problems” were related to repetitive irritation of the esophagus (from patients getting pills stuck in their throats), taking fewer pills each week could reduce the attending GI problems.¹² Thus, the district court clearly erred in finding any significant difference between the claimed invention and the two articles as to this type of GI problem.

The district court found a second adverse GI side-effect related to the size of the dose, which Merck argued gave rise to “the expectation by physicians in the field during 1996–1997 that alendronate sodium at doses over 20 mg would not be well-tolerated in the prevention and treatment of osteoporosis.” *Merck*, 288 F.Supp.2d at 624; *see also id.* at 622–23, 627–30 (discussing Chesnut study). Neither the ’329 patent nor the *Lunar News* articles explain how a higher once-weekly dosing regimen would avoid this set of dose-related adverse side effects. The ’329 patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent. The only data provided in the ’329 patent was generated in beagles, an experiment discredited at trial and disregarded by the district court in its decision. So while the district court may be correct in finding the *Lunar News* articles may have invited skepticism based on concerns for dose-related GI problems, the claimed invention adds nothing beyond the teachings of those articles. Thus, the district court

clearly erred in finding any difference between the claimed invention and the articles on this point.

The district court’s only remaining distinction between the claimed invention and the two *Lunar News* articles goes to the probative value of the articles. The trial court wrote that it “[was] not persuaded that the two *Lunar News* articles, not published in peer-reviewed journals or authored by one skilled in the art, either alone or in combination, overcame the serious side effect concerns associated with higher dosage units of alendronate sodium.” *Merck*, 288 F.Supp.2d at 629. Although these indicia of reliability—whether a study is peer-reviewed, and the credentials of the author—properly go to weight when the trial court has not excluded evidence as unreliable and irrelevant, the district court’s reliance on these factors to distinguish Merck’s claimed invention is, again, misplaced. First, as noted above, these factors provide no relevant distinction between the articles and the claimed invention because the ’329 patent also fails to explain how its higher dosing would overcome these dose-related side-effects. Second, as explained below the district court’s finding the author of the *Lunar News* articles not skilled in the relevant art is inconsistent with the court’s own definition of the relevant art. Thus, the extent to which the district court discounts the probative value of the two articles based on the credentials of the author calls for closer scrutiny and

12. As the ’329 patent states:

[I]t is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, *particularly esophageal effects*, compared to the administration of a low relative dosage at a high relative dosing frequency. . . . Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffer-

ing from or are susceptible to upper gastrointestinal disorders, e.g., gastrointestinal reflux disease (i.e. “GERD”), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

’329 patent, col. 3, l. 57—col. 4, l. 13 (emphasis added).

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casts doubt on the findings that depend on this reasoning.

In short, the district court clearly erred in distinguishing the claimed invention from the two *Lunar News* articles offered as section 103 prior art. Contrary to the district court's findings, these articles support the conclusion that Merck's claims 23 and 37 are invalid as obvious.

For similar reasons we find the district court's characterization of the scope and content of the prior art favors invalidating claims 23 and 37 as obvious. The district court described its larger task as identifying "a showing of the teaching or motivation to combine prior art references." *Merck*, 288 F.Supp.2d at 625 (quoting *In re Gartside*, 203 F.3d 1305, 1319 (Fed.Cir. 2000)). But as shown above, in this case the *Lunar News* articles contain the relevant teaching of the weekly dosing claimed in the '329 patent. The "specific combination" of elements in claims 23 and 37 differs from the disclosure in the *Lunar News* articles only in terms of a minor difference in the dosage; without this difference, the *Lunar News* articles would anticipate claims 23 and 37 under section 102. For the *Lunar News* articles to render claims 23 and 37 obvious, the district court need only have found a suggestion or motivation to modify the dosages from those in the articles to those in the claims. See, e.g., *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed.Cir.2000). But as noted above, Merck's own inventors admit the difference in dosing amount is obvious. If anything, concern over dosing amount suggests lowering the weekly dosage—from 80 to 70 mg, and from 40 to 35 mg, just as Merck did. The district court thus clearly

erred to the extent it found lacking any motivation to combine existing knowledge with the *Lunar News* articles to reach the claimed invention.

The district court failed to ascertain the required motivation to combine references to achieve the claimed invention, and it ignored the plain teachings of the *Lunar News* articles. As the court stated, "the issue is when viewing the mosaic of prior art, whether those of ordinary skill in the art would have had the motivation to formulate a once-weekly seven-fold daily dose of alendronate, despite safety concerns." *Merck*, 288 F.Supp.2d at 626.

The *Lunar News* articles had clearly suggested the once-weekly dosing. They did so, as noted above, and as described in the '329 patent, to avoid or minimize problems related to dosing frequency. And as shown above, the district court itself found this particular set of problems were of greatest concern in the art. Indeed, to the extent the district court finds Merck's weekly-dosing idea non-obvious because it went against prevailing wisdom, the court must still explain why Merck and not Dr. Mazess should get credit for the idea. Because Merck's idea added nothing to what came before, the district court's answer comes down to nothing more than the credentials of the authors. In this case that difference is not enough to avoid invalidating the claims.¹³

The district court answered its own question incorrectly, because its analysis of the prior art fails to credit its own distinction between the "safety concerns" from dosing frequency and dosing amount. As noted above, the claimed invention does not address the problems with the dosing

13. Although the court is unsure whether an obviousness ruling can ever turn solely on the credentials of the inventors and prior art authors, where the prior art has been admitted, it need not decide that question here. As

noted below, by the district court's own functional definition (if not its actual finding) Dr. Mazess was one of skill in the art, and the *Lunar News* was widely circulated in the field.

amount, but only the more widespread problems of the dosing frequency. The court's review of the scope and content of the prior art itself focuses on this concern with "prolonged contact of the drug with the esophagus." *Merck*, 288 F.Supp.2d at 627. This understanding of the prior art does not support a conclusion that the claimed invention as a whole was non-obvious in view of the prior art. See *Para-Ordnance Mfg. v. SGS Importers Int'l Inc.*, 73 F.3d 1085, 1087 (Fed.Cir. 1995); *In re Kaslow*, 707 F.2d 1366, 1374 (Fed.Cir.1983). Insofar as the district court relied on safety concerns related to dosing frequency, the prior art favors the conclusion that taking pills once a week was obvious.

Thus, the scope and content of the prior art confirms that the invention claimed in claims 23 and 37 would have been obvious in view of the *Lunar News* articles. To the extent the district court interpreted the scope of the prior art otherwise, that was clear error.

We likewise find clear error in the district court's conclusion that Dr. Mazess was not skilled in the relevant art. The district court failed to credit the evidence showing Mazess's *Lunar News* was widely distributed among those working in the field of osteoporosis. Moreover, while we recognize the importance academic or professional training plays in establishing expert qualifications or the probative value of a section 103 reference, we think the district court failed to give proper credit to the fact that Dr. Mazess was an expert in osteoporosis. In focusing on Dr. Mazess's academic training, the district court ignored its own finding that one of skill in the art would be someone "working in the field of, or doing research on, osteoporosis." Thus, the district court erred in dismissing or minimizing the probative value of the *Lunar News* articles.

Finally, the district court erred in its weighing of secondary considerations of non-obviousness. Although the district court correctly found Merck's once-weekly dosing of Fosamax was commercially successful, in this context that fact has minimal probative value on the issue of obviousness. *Merck*, 288 F.Supp.2d at 629–30. Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or "nexus" between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious. See *Graham*, 383 U.S. at 17–18, 86 S.Ct. 684 ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."); *McNeil-PPC, Inc. v. L. Per-rigo Co.*, 337 F.3d 1362, 1370 (Fed.Cir. 2003).

[13] That rationale has no force in this case. In *Graham* the Supreme Court relied on the reasoning from a law review note discussing commercial success. See *Graham*, 383 U.S. at 17–18, 86 S.Ct. 684, citing Note, *Subtests of "Nonobviousness": A Nontechnical Approach to Patent Validity*, 112 U. Pa. L.Rev. 1169, 1175 (1964). The article suggested "[t]he possibility of market success attendant upon the solution of an existing problem may induce innovators to attempt a solution. If in fact a product attains a high degree of commercial success, there is a basis for inferring that such attempts have been made and have failed." As our predecessor

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court explained in *In re Fielder*, 471 F.2d 640, 644 (C.C.P.A.1973), “[t]hese rationales, presumably approved by the [Supreme] Court, tie commercial success and the like directly to the practical, financial source of impetus for research and development.” But that chain of inferences fails on these facts. Although commercial success might generally support a conclusion that Merck’s claimed invention was non-obvious in relation to what came before in the marketplace, the question at bar is narrower. It is whether the claimed invention is non-obvious in relation to the ideas set forth in the *Lunar News* articles. Financial success is not significantly probative of that question in this case because others were legally barred from commercially testing the *Lunar News* ideas. Dr. Mazess, for example, could not put his ideas to practice in 1996—he could only exhort Merck to try it. They did.

In this case Merck had a right to exclude others from practicing the weekly-dosing of alendronate specified in claims 23 and 37, given (1) another patent covering the administration of alendronate sodium to treat osteoporosis, U.S. Pat. No. 4,621,077 (issued Nov. 4, 1986); and (2) its exclusive statutory right, in conjunction with FDA marketing approvals, to offer Fosamax at any dosage for the next five years. 21 U.S.C. § 355(c)(3)(D)(ii) (2000). Because market entry by others was precluded on those bases, the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak. Although commercial success may have probative value for finding non-obviousness of Merck’s weekly-dosing regimen in some context, it is not enough to show the claims at bar are patentably distinct from the weekly-dosing ideas in the *Lunar News* articles. Thus, we conclude the district court misjudged this factor as confirming its conclusion of non-obviousness.

In short, we find the relevant *Graham* factors establish claims 23 and 37 of the ’329 patent are obvious in view of the April 1996 and July 1996 *Lunar News* articles. Thus, we reverse the district court and hold claims 23 and 37 invalid.

III. CONCLUSION

We reverse the district court’s claim construction and hold that “about” should be construed consistently with its ordinary meaning of “approximately.” In addition, we vacate the district court’s determination that the ’329 patent was not invalid as obvious. We hold claims 23 and 37 invalid as obvious and not infringed. The district court’s judgment of infringement is therefore

REVERSED.

COSTS

No costs.

RADER, Circuit Judge, dissenting.

This case shows the consequences of paying only lip service to the often-cited, but rarely-followed lexicographer rule and the basic jurisprudential principle of according trial courts proper deference.

Elect the Lexicographer Option
at Your Own Risk

With this court’s claim constructions waver between the plain meaning rule (often a subtle way for judges to impose their own semantic subjectivity on claim terms, *see, e.g., K-2 v. Salomon*, 191 F.3d 1356 (Fed.Cir.1999) (“permanent” affixation of the wheels to the skate boot in the context of in-line skates did not include a bolt that could only be reached by tearing apart the shoe)) and the “specification über alles” rule (often a way for judges to import limitations not included in the claim, *see, e.g., Phillips v. AWH Corp.*, 363 F.3d 1207,

1213–14 (Fed.Cir.2004), *vacated, reh'g en banc granted*, 376 F.3d 1382 (Fed.Cir. July 21, 2004)), a patent applicant might suppose that the best option to define the scope of the claim language might be the lexicographer rule. Under the lexicographer rule, an inventor acts as an independent lexicographer and can even give claim terms a meaning “inconsistent with its ordinary meaning.” *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1347 (Fed.Cir.2003) (citing *Teleflex, Inc. v. Ficoso N. Am. Corp.*, 299 F.3d 1313, 1325–26 (Fed.Cir.2002)); *see also Teleflex*, 299 F.3d at 1325 (“[A]n inventor may choose to be his own lexicographer if he defines the specific terms used to describe the invention ‘with reasonable clarity, deliberateness, and precision.’” (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed.Cir.1994))). Indeed, this court often acknowledges that an applicant, acting as a lexicographer, may define “black” as “white.” *See Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1563 (Fed.Cir.1990) (“It is a well-established axiom in patent law that a patentee is free to be his or her own lexicographer and thus may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings.”); *see also, e.g., Int’l Rectifier Corp. v. IXYS Corp.*, 361 F.3d 1363, 1373 (Fed.Cir.2004) (patentee defining “annular,” which ordinarily means in the shape of a ring, to describe structures that are not circular or curved, but polygonal). In this case, the patentee used the lexicographer rule to define a lengthy phrase. In its definition, the patentee defined the phrase with precise values. The patentee’s definition, however, fell five letters short of success because the phrase included the word “about.” This court seized on that word, gave it an ordinary meaning, and cast aside the lexicographer rule without a convincing explanation. Moreover, this court overturned the result of a lengthy district court trial

for the sole reason that the trial court applied this court’s lexicographer rule. I find it hard to explain to the district court how it erred by following this court’s rules.

The disputed term in claim 23 of the ’329 patent is the phrase “about 70 mg of alendronate monosodium trihydrate, on an alendronic acid basis.” Similarly, the disputed term in claim 37 is the phrase “about 35 mg of alendronate monosodium trihydrate, on an alendronic acid basis.” Teva contends that this court should parse out one word in that phrase, “about,” and accord that single word its ordinary meaning of “approximately.” Merck, on the other hand, contends that the term “about” is inseparable from the entire phrase, which it defines under the lexicographer rule to account for the variability in the active ingredient weight that would result from the use of a salt of alendronic acid.

The specification shows the proper interpretation of the disputed phrase. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996) (“The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.”). In the specification of the ’329 patent, the patentee exercised the lexicographer option and defined the disputed phrase as follows:

Because of the mixed nomenclature currently in use by those o[f] ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless otherwise indicated herein. For example, the phrase “about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis” means that the amount of the bisphosphonate

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compound selected is calculated based on 70 mg of alendronic acid.

'329 patent, col. 10, l. 65—col. 11, l. 8.

In a passage that classically invokes this court's lexicographer doctrine, the patentee clearly, deliberately, and precisely defined the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis." The patentee set forth that entire term with quotations, including the word "about" and then stated unambiguously that the "phrase . . . means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid." '329 patent, col. 11, ll. 2—8 (emphases added). The choice of the words "phrase" and "means," combined with the use of quotation marks to set the phrase off from the rest of the sentence, unmistakably notify a reader of the patent that the patentee exercised the option to define the entire phrase without respect to its ordinary meaning as understood by one of ordinary skill in the art at the time of the invention. See *Multiform Desiccants, Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir.1998).

To underscore the choice to define the phrase as a lexicographer, the patentee explains the reason that this phrase needs definition—"[b]ecause of the mixed nomenclature currently in use by those of ordinary skill in the art." '329 patent, col. 10, ll. 65–66. Therefore, even a casual reader, let alone one with skill in this art, would immediately recognize that the patentee intended to avoid any ambiguity inherent in "mixed nomenclature" by explicitly defining the entire phrase. See *Paulsen*, 30 F.3d at 1480 ("Where an inventor chooses to be his own lexicographer and to give terms uncommon meanings, he must set out his uncommon definition in some man-

ner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change." (quoting *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1388 (Fed.Cir.1992))).

The language of this definition explains further the scientific reason that an express definition is necessary. Alendronate monosodium trihydrate is a bisphosphonate selected from the group consisting of alendronic acid, pharmaceutically acceptable salts thereof, and mixtures thereof. A salt or a mixture may require a different weight to achieve the same number of bisphosphonate molecules present in 70 mg of alendronate.

The patentee did not leave this difference vague, however, but instructed that the precise dose in claim 23—"about 70 mg of alendronate monosodium trihydrate, on an alendronic acid basis"—means that the amount of alendronate monosodium trihydrate is calculated based on 70 mg of alendronic acid. Similarly, the disputed language of claim 37—"about 35 mg of alendronate monosodium trihydrate, on an alendronic acid basis"—means that the amount of alendronate monosodium trihydrate is calculated based on 35 mg of alendronic acid. The word "about" in the defined phrase takes into account the variability of the weight of the active ingredient that would result from using different salts of alendronic acid in the tablets, instead of the acid itself. In other words, a heavier salt would require more by weight to achieve the same number of alendronate molecules. For example, *about* 70 mg of alendronate sodium, on an alendronic acid active basis, contains the same number of molecules of alendronate as 70 mg of alendronic acid, regardless of the actual weight of the alendronate sodium in the tablet.

With respect to the word "about," the patentee included that word in the entire

phrase expressly defined in the specification and set off by quotation marks. Therefore, this court cannot, without disturbing the patentee's express definition of the entire phrase, abstract that term out of its context and supply an ordinary meaning. Thus, by abstracting "about" out of the patentee's express definition, this court's opinion defeats the patentee's choice of words, punctuation, and phraseology and instead extracts a single word from its context in the phrase. Accordingly, the majority rewrites the express definition either by moving the word "about" outside of the quotation marks of the defined phrase or by inserting the word "about" into the definitional portion of the sentence so that it would read "the amount of the bisphosphonate compound is calculated based on *about* 70 mg of alendronic acid." If the patentee had chosen either of those two phraseologies, the majority opinion might be correct in its analysis. But because the patentee did not, this court cannot give any principled reason that the district court erred in applying the lexicographer rule. Contrary to this court's rules, this opinion rewrites the specification and substitutes language not chosen by the patentee. *See, e.g., Chef Am., Inc. v. Lamb Weston, Inc.*, 358 F.3d 1371, 1374 (Fed.Cir.2004) (repeating the well-established rule that "courts may not redraft claims").

Throughout the patent, the applicant remained faithful to the disputed phrases in claims 23 and 37 consistent with the specified lexicography, thus completely dispelling any notion of ambiguity in the term "about." In particular, Examples 7 and 8 corroborate the express definition. Example 7 states that "[t]ablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following weights of ingredients" and lists alendronate monosodium trihydrate requiring a mass of 45.68 mg. *See* '329 patent, col. 19, ll. 14—21. Similarly, exam-

ple 8 states that "[a] liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following weights of ingredients" and lists alendronate monosodium trihydrate having a mass of 91.35 mg. *Id.* at col. 19, ll. 44—52. In these examples, the applicant supplied an exact weight that equates with "about 70 mg of alendronate . . . on an alendronic acid active basis." Accordingly, the district court did not err in construing "the disputed claim terms 'about 70/35 mg' to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories." *Merck*, 288 F.Supp.2d at 616. The district court followed this court's rules.

Deference to Trial Courts: Time for "Truth in Advertising?"

This is the classic "close case," so close in fact that ultimately two federal judges (one of whom conducted an entire bench trial on this issue) and the United States Patent and Trademark Office agreed with Merck & Co., and two federal judges agreed with Teva Pharmaceuticals. The United States District Court of Delaware tried this case from March 4—7, 2003, then issued a 75-page opinion analyzing the claims and arguments in consummate and accurate detail. *Merck & Co. v. Teva Pharms. USA, Inc.*, 288 F.Supp.2d 601 (D.Del.2003). This court received the typical briefs from the parties, an appendix containing selected portions of the record, and heard a total of approximately thirty minutes of argument by the parties on the issues before this court. Despite the district court's superior tools and time to evaluate the complete record, to hear and inquire from expert and fact witnesses, to delve into countless related details, to probe the scientific and semantic context, and to entertain argument as

MERCK & CO. v. TEVA PHARMACEUTICALS USA**1381**

Cite as 395 F.3d 1364 (Fed. Cir. 2005)

long as necessary for clarity, this court with its reading three briefs before its half-hour hearing becomes enamored with its own analysis of a very close issue and reverses the district court.

This court often hears criticism from district court judges that its reversal rate on claim construction issues far exceeds that of other circuit courts. *See, e.g.,* Symposium, *The Law, Technology and the Future of the Federal Circuit: A Panel Discussion: Claim Construction from the Perspective of the District Judge*, 54 Case W. Res. L.Rev. 671 (2003) (*Symposium I*) (district judges discussing problems with this court's high reversal rate on claim construction issues); *see* Gregory J. Wallace, Note, *Toward Certainty and Uniformity in Patent Infringement Cases after Festo and Markman: A Proposal for a Specialized Patent Trial Court with a Rule of Greater Deference*, 77 S. Cal. L.Rev. 1383, 1391 (2004) (discussing various studies regarding this court's reversal rate on claim construction issues). In response, nearly every judge on this court has publicly professed to accord some level of deference to district courts regardless of this court's *de novo* review of claim construction issues. *See, e.g.,* *Symposium I* at 680 (a district court judge stating "I have certainly heard a number of federal circuit judges agree, that the CAFC gives some deference to a well-reasoned opinion,

as a practical matter"); Symposium, *The Past, Present and Future of the Federal Circuit: Judicial Constellations: Guiding Principles as Navigational Aids*, 54 Case W. Res. L.Rev. 757, 761 (2004) (judge of the Federal Circuit stating: "Review is really not *de novo* after all. It is unfortunate that there is no label in between *de novo* and clear error review. Functionally, claim construction falls in this middle ground."). Either the Federal Circuit accords deference in accordance with its public protestations or it does not in accordance with its legal standard barring any deference. If the former, this court has a "truth in advertising" problem. Its actual practice clashes with its professed legal duty. If the latter, this court has a different kind of "truth in advertising" problem.

In this case, this court eschews all deference, a particularly striking choice in the face of a very close case and a district court whose diligent and intelligent process and resolution earned more respect than it received. I am not entirely sure which aspect of the "truth in advertising" problem this case illustrates, but it certainly makes any protestations of deference in fact sound rather hollow.



EXHIBIT J

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

**PROVISIONAL APPLICATION FOR
PATENT COVER SHEET**

ATTORNEY DOCKET NO.:
1662/62201

Address to:
Commissioner for Patents
Washington, D.C. 20231
Box Provisional Application

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Inventor(s) and Residence(s) (city and either state or foreign country):

FLESHNER-BARAK, Moshe - Hefetz Mordechai 15, Petach Tikva, Israel
LERNER, E. Itzhak - Wolfson 32, Petach Tikva, Israel
ROSENBERGER, Vered - Ms. Landau 3, Givat Masuah, Jerusalem, Israel

For : **METHOD OF INCREASING BIOAVAILABILITY OF
ALENDRONATE OR OTHER BISPHOSPHONATES BY
PREDOSE ADMINISTRATION OF ALFACALCIDOL**

1. 13 sheets of specification and abstract
2. 0 sheets of drawing
3. Please charge the required application filing fee of **\$160.00 (large entity)**, and any other fees that may be required, to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**. A duplicate of this sheet is enclosed.
4. Please direct all communications relating to this application to:

Steven J. Lee, Esq.
KENYON & KENYON
One Broadway
New York, New York 10004
(212) 425-7200 (phone)
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5. This invention was not made by an agency of the United States Government or under a contract with an agency of the United States Government.

Respectfully submitted,

Dated: December 16, 2002

By:

John B. Starr, Jr. (Reg. No. 44,474)

Express Mail #EL828251306US

METHOD OF INCREASING BIOAVAILABILITY OF ALENDRONATE OR OTHER BISPHOSPHONATES BY PREDOSE ADMINISTRATION OF ALFACALCIDOL

5

FIELD OF THE INVENTION

The present invention relates to a method of increasing the bioavailability of bisphosphonates such as alendronate by administering to the recipient a predose of
10 alfacalcidol (1 α -hydroxyvitamin D₃) at least six hours before the administration of the therapeutic dose of the bisphosphonate.

BACKGROUND OF THE INVENTION

Treatment of osteoporosis, metastatic bone disease, and Paget's disease can
15 benefit from improvements in controlled gastric release and multiple dose delivery technology. Bisphosphonates such as sodium alendronate, risedronate, etidronate, zoledronic acid and tiludronate are commonly prescribed drugs for treatment of these diseases. Despite their benefits, bisphosphonates suffer from very poor oral bioavailability. Alendronate has less than 1% bioavailability. Gert, B. J.; Holland,
20 S.D.; Kline, W.F.; Matuszewski, B. K.; Freeman, A.; Quan, H.; Lasseter, K. C.; Mucklow, J. C.; Porras, A. G. "Studies of The Oral Bioavailability of Alendronate," *Clinical Pharmacology & Therapeutics* **1995**, 58, 288-298. Its absorption is inhibited by foods and beverages other than water. *Id.* Side effects experienced by patients who have taken alendronate include irritation of the upper gastrointestinal mucosa.
25 Liberman, U. A.; Hirsch, L. J.; "Esophagitis and Alendronate" *N. Engl. J. Med.*, **1996**, 335, 1069-70. This irritation can lead to more serious conditions. *Physicians' Desk Reference*, Fosamax, Warnings.

Alendronate is best absorbed from the upper GI tract (duodenum and jejunum). Lin, J. H. "Bisphosphonates: A Review of Their Pharmacokinetic
30 Properties," *Bone*, **1996**, 18, 75-85; Porras, A. G.; Holland, S. D.; Gertz, B. J.; "Pharmacokinetics of Alendronate," *Clin. Pharmacokinet* **1999**, 36, 315-328. Alendronate is best absorbed at a pH of ~6. Gert, B. J.; Holland, S.D.; Kline, W.F.; Matuszewski, B. K.; Freeman, A.; Quan, H.; Lasseter, K. C.; Mucklow, J. C.; Porras, A. G. "Studies of The Oral Bioavailability of Alendronate," *Clinical Pharmacology &*
35 *Therapeutics*, **1995**, 58, 288-298. As discussed in commonly-assigned, co-pending application Serial No. 09/770,898, controlled gastric release of alendronate would allow for extended delivery of the drug to the duodenum and jejunum parts of the intestine and should result in improved bioavailability, and thus allow lower dosing and less irritation.

In addition to bisphosphonate therapy, options in the treatment of osteoporosis include hormone replacement therapy and calcium supplementation therapy.

Kleerekoper, M., Schein, J. R. "Comparative Safety of Bone Remodeling Agents with A Focus on Osteoporosis Therapies," *J. Clin. Pharmacol.* **2001**, *41*, 239. Increased

5 calcium levels can potentially improve the state of bone mineralization in patients with osteoporosis. Over the last thirty years, calcium supplementation, along with vitamin D or vitamin D analogues such as calcitriol, has been one of the options for treating the problems of osteoporosis. Cannigia, A., Vattimo, A. "Effects of 1,25

10 *Clin. Endocrinol.*, **1979**, *11*, 99; Riggs, B. L., Nelson, K. L. "Effect of Long Term Treatment with Calcitriol on Calcium Absorption and Mineral Metabolism in Postmenopausal Osteoporosis," *J. Clin. Endocrinol. Metab.* **1985**, *61*, 457; Reid, I. R.,

Ames, R. W., Evans, M. C., Gamble, G. D., Sharpe, S. J. "Long Term Effects of Calcium Supplementation on Bone Loss and Fracture in Post-menopausal Women, a

15 Randomized Controlled Trial, *Am. J. Med.*, **1995**, *98*, 331. Calcitriol (1,25-dihydroxyvitamin D₃) is a vitamin D analogue that is active in the regulation of the absorption of calcium from the gastrointestinal tract. *Physicians' Desk Reference*, Rocaltrol Oral Solution, Description. Calcitriol is the biologically active form of vitamin D₃ and stimulates intestinal calcium transport. *Merck Index*, 12th Ed., 1681.

20 Calcitriol is rapidly absorbed from the intestine and reaches peak serum concentrations within three to six hours after ingestion. *Physicians' Desk Reference*, Rocaltrol Oral Solution, Pharmacokinetics. Calcitriol is used to treat calcium deficiency.

Over the past several years, successful trials have been performed that confirm

25 that there is a synergistic effect in using a combined therapy of calcitriol and bisphosphonates. Frediani, B., Allegri, A., Bisogno, S., Marcolongo, R. "Effects of Combined Treatment with Calcitriol Plus Alendronate on Bone Mass and Bone Turnover in Postmenopausal Osteoporosis-Two Years of Continuous Treatment,"

Clin. Drug Invest. **1998**, *15*, 223; Masud, T., Mulcahy, B., Thompson, A. V.,

30 Donnelly, S., Keen, R. W., Doyle, D. V., Spector, T. D., "Effects of Cyclical Etidronate Combined with Calcitriol Versus Cyclical Etidronate Alone on Spine and Femoral Neck Bone Mineral Density in Postmenopausal Women," *Ann. Rheum. Dis.*, **1998**, *57*, 346; Malvolta, M., Zanardi, M., Veronesi, M., Ripamonti C., Gnudi, S.

"Calcitriol and Alendronate Combination Treatment in Menopausal Women with Low Bone Mass," *Int. J. Tissue React.* **1999**, *21*, 51; Nuti, R., Martini, G., Giovani, S., Valenti, R. "Effect of Treatment with Calcitriol Combined with Low-dosage Alendronate in Involutional Osteoporosis," *Clin. Drug Invest.*, **2000**, *19*, 56. The

goal of the combined therapy trials is to improve therapeutic results and lower the dosage of the two drugs. In these trials the drugs were given individually. International Publication WO 2001/028564 discloses a tablet containing a combination of calcitriol and alendronate in a particular range of ratios of the two drugs.

Although there has been a recognition of the benefits of combination therapy in the treatment of osteoporosis, metastatic bone disease and Paget's disease, there remains a need for an improved dosing regimen for a bisphosphonate and a calcium transport stimulator in order to fully realize the advantages of combined therapy.

In a co-pending patent application (U.S. provisional 60/305,913 filed 17/7/01 and U.S. application Serial No. 10/196,766 filed 17/7/02), the current inventors claimed the method of improving the absorption of bisphosphonates by predosing with a vitamin D analogue 2 to 6 hours before dosing the alendronate. While such administration is useful, it does not allow for overnight predosing unless the vitamin D analogue and the bisphosphonate are part of a single delivery system.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a method of increasing the bioavailability of a bisphosphonate, especially alendronic acid or pharmaceutically acceptable salts thereof, in a mammal to which such bisphosphonate is administered which includes the steps of administering to the mammal a predose of a vitamin D analogue, especially alfacalcidol, and, at least about six hours thereafter, administering a therapeutic dose of the bisphosphonate.

In another aspect, the present invention relates to a method of increasing the bioavailability of a bisphosphonate, wherein the bisphosphonate is selected from the group which includes an alendronate, a risedronate, an etidronate, a zoledronate and a tiludronate, or their acids or pharmaceutically acceptable salts thereof, especially alendronate, in a mammal to which such bisphosphonate is administered which includes the steps of administering to the mammal a predose of a vitamin D analogue, wherein the vitamin D analogue is selected from the group which includes calcitriol, alfacalcidol, 24,25-dihydroxy vitamin D₃, and calcifediol, especially alfacalcidol, wherein the predose of alfacalcidol is at least about 0.1 µg, and especially between about 0.1 µg and about 10 µg, and, at least about six hours thereafter, administering a therapeutic dose of alendronate.

In yet another aspect, the present invention relates to a method of increasing the bioavailability of alendronate, in a mammal to which such bisphosphonate is administered which includes the steps of administering to the mammal a predose of

alfacalcidol, wherein the predose of alfacalcidol is at least about 0.1 μ g, and especially between about 0.1 μ g and about 10 μ g, and, at least about six hours thereafter, especially between at least about 6 hours and about 12 hours thereafter, and most especially between at least about 6 hours and about 10 hours thereafter, administering a therapeutic dose of alendronate, wherein the therapeutically effective dose of alendronate administered is between about 1 mg and about 100 mg, and especially between about 10 mg and about 70 mg.

In a still further aspect, the present invention relates to a method of increasing the bioavailability of alendronate, in a mammal to which such bisphosphonate is administered which includes the steps of administering to the mammal a predose of alfacalcidol, wherein the predose of alfacalcidol is at least about 0.1 μ g, and especially between about 0.1 μ g and about 10 μ g, and most especially between about 0.2 μ g and about 2 μ g, wherein the predose of alfacalcidol is administered at night, especially between about 8 P.M. and about midnight, and, between at least about 6 hours and about 10 hours thereafter, the therapeutic dose of alendronate is administered, especially before the first meal of the next day, and most especially between about 6 A.M. and about 10 A.M., wherein the therapeutically effective dose of alendronate administered is between about 1 mg and about 100 mg.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of combination drug therapy to increase the bioavailability of a bisphosphonate that includes the steps of administering a predose of a calcium transport stimulator, especially alfacalcidol, followed by administration of a bisphosphonate calcium resorption inhibitor at least about 6 hours after the calcium transport stimulator is administered. The present invention takes advantage of the fact that a calcium transport stimulator depletes the calcium concentration in the intestine, in addition to its recognized benefit of increasing calcium in the blood. Complexation of a bisphosphonate with calcium in the gut inhibits its absorption. The depletion of calcium results in improved absorption of the bisphosphonate in the intestine. When a bisphosphonate calcium resorption inhibitor is delivered to the upper small intestine after delivery of a vitamin D analogue that is a calcium transport stimulator, absorption of the bisphosphonate will be increased. The bisphosphonate will enter an environment partially depleted in calcium due to the transport activity of the vitamin D analogue. This depleted calcium environment will thus allow a higher absorption of the bisphosphonate, thereby allowing a dose lowering in addition to the dose lowering caused by the synergistic effect of the bisphosphonate and vitamin D analogues that occurs after

reaching the bloodstream.

In one embodiment, the present invention provides a method of increasing the bioavailability of a bisphosphonate by administering a combination drug regimen that includes the steps of administering a predose of a vitamin D analogue and, about at
 5 least 6 to about 12 hours later, administering a therapeutic dose of a bisphosphonate.

As used herein, bioavailability means "the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action;" "the fraction of drug absorbed as such into the systemic circulation." *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th
 10 Ed., 2001, 5, 18 (eds. Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman; McGraw Hill Pub.). An approximate estimation of oral bioavailability may be based on secondary information (e.g., urinary excretion or the amount of the drug excreted unchanged in the urine, expressed as a percentage of the administered dose). *Id.* at 1918.

The present invention includes the step of administering of a predose of a vitamin D analogue. The skilled artisan will understand that a predose is the dose of the vitamin D analogue that is administered at some time prior to administration of the therapeutic dose of the bisphosphonate. A predose is a dose typically between about 0.1 µg and about 10 µg of a vitamin D analogue.

The vitamin D analogues useful in the practice of the present invention are calcium transport stimulators. Calcium transport stimulators facilitate the intestinal absorption of calcium. *Id.* at 1728. Vitamin D analogues useful in the practice of the present invention are structural analogues of the hormone, vitamin D. Examples of vitamin D analogues useful in the practice of the present invention include calcitriol, alfacalcidol, 24,25-dihydroxy vitamin D₃, and calcifediol. The most preferred vitamin
 25 D analogue useful in the practice of the present invention is alfacalcidol. Alfacalcidol may be dosed in any amount that results in increased intestinal absorption of the bisphosphonate compared to an equal dose of the bisphosphonate administered without alfacalcidol. A preferred dose range of alfacalcidol is from about 0.1 µg to about 10 µg, most preferably between about 0.2 µg to about 2 µg.

Alfacalcidol, or 1α-hydroxyvitamin D₃, is a synthetic analogue of calcitriol, the hormonal form of Vitamin D₃. Like calcitriol, alfacalcidol stimulates intestinal calcium absorption. However, there is a delay of several hours between the time when the alfacalcidol enters the intestine and when the blood calcium level peaks.
 35 Maximum calcium depletion in the intestine should coincide with the peak in blood calcium level. Therefore, in order to release the bisphosphonate into an environment of minimum calcium, administration of the predose of alfacalcidol should be of a

sufficient time interval before administration of the bisphosphonate dose to provide the maximum increase in bisphosphonate bioavailability. The maximum increase in bisphosphonate bioavailability is observed when the time interval between administration of the predose of alfacalcidol and the bisphosphonate dose is at least 6 hours, preferably between at least 6 hours and about 14 hours, more preferably between at least 6 hours and 12 hours and especially between at least 6 hours and about 10 hours.

This time interval between predosing with alfacalcidol and administration of the bisphosphonate dose allows for a convenient dosage regimen in which the predose of alfacalcidol can be administered between 8 P.M. and midnight and the bisphosphonate dose can be administered between 6 A.M. and 10 A.M. on the following morning. By administration of the predose of alfacalcidol at night before bed time and the therapeutic dose of the bisphosphonate in the morning before the first meal, one obtains maximum increase in bisphosphonate bioavailability with maximum convenience in dosing. This finding allows for a significant improvement in the convenience of the dosing regimen to obtain the enhanced bisphosphonate bioavailability.

The bisphosphonates useful in the practice of the present invention are calcium resorption inhibitors. Examples of bisphosphonates useful in the practice of the present invention include alendronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "alendronate"), risedronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "risedronate"), etidronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "etidronate"), zoledronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "zoledronate"), and tiludronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "tiludronate"). The skilled artisan will recognize that pharmaceutically acceptable salts can exist as solvates, e.g., hydrates. The bisphosphonates may be provided in any pharmaceutically acceptable salt or acid form, salts being generally preferred because they cause less membrane irritation. Alendronate is preferably provided as a monosodium salt monohydrate or trihydrate. Risedronate is preferably provided as a monosodium salt hemipentahydrate. Etidronate and tiludronate are preferably provided as hydrated or anhydrous disodium salts. Zoledronate is preferably provided as a disodium salt tetrahydrate or trisodium salt hydrate.

The most preferred bisphosphonate of the present invention is alendronate. The preferred therapeutic dose of alendronate is between about 1 mg and about 100

mg, most preferably between about 10 mg and about 70 mg.

Administration of the vitamin D analogue in the combination drug regimen of the present invention can be by any means known in the art. Solid oral dosage forms are preferred.

5 Administration of the bisphosphonate in the combination drug regimen of the present invention can also be by any means known in the art. Administration *via* a solid oral dosage form is preferred. The solid oral dosage form can be of the conventional type well known in the art (e.g., Fosamax®).

10 Having thus described the invention with reference to certain preferred embodiments, it is further illustrated by the following non-limiting example.

EXAMPLE

In-Vivo Study on Improving the Bioavailability of Alendronate: Effect of Varying Predose Intervals of Alfacalcidol in a Combination Drug Regimen with Alendronate.

5 An *in vivo* study in an animal model was conducted to determine whether alfacalcidol, administered in varying predose intervals in combination therapy with alendronate increased the bioavailability of alendronate compared with the administration of alendronate alone.

10 Six female beagle dogs, each approximately 2 years old and weighing approximately 9 kg were the animal models in this study. The same animals were used in each of five separate treatment sessions lasting 34-42 hours each, the duration of each session depending on the predose test interval being measured. The same drugs at identical dosages were administered in every treatment, *viz.*, alfacalcidol (ALPHA D3®, 1.0 µg gel capsule; TEVA) was the Vitamin D₃ analogue administered
15 as the predose drug and alendronate sodium (Fosalan®, 10 mg tablet, Merck, Sharp & Dohme) was the bisphosphonate administered as the therapeutic drug. There was a 7 day wash-out period between sessions. The clinical state of each dog was checked within 48 hours prior to each treatment session and again after the last session. In each session the animals were dosed in the fasted state (n.p.o. 10-12 hours). The dogs
20 were fed a standardized meal (canned Bonzo meat, 1 full can, 425 grams) four hours after administration of the therapeutic dose of alendronate.

During each session, the dogs were housed in steel metabolic cages. Urine samples were recovered from the bottom of the metabolic cages. At each collection point, two representative samples of urine (*ca.* 5 ml each) were taken in capped
25 polypropylene vials and immediately frozen at -20° C. The remainder of the sample was frozen and retained.

Urine samples were analyzed for alendronate by HPLC with fluorescence detection (Anapharm, Inc., Quebec, Canada).

30 In each session, the predose study drug, alfacalcidol, was administered in the A.M., in the fasted state, with 10-20 ml tap water to facilitate swallowing. During the monitoring (collection) period of each session, dogs were hydrated *via* gastroesophageal tube with 300 ml tap water on the evening prior to initiation of each testing session and subsequently, with 150 ml tap water every two hours post-administration of the therapeutic dose of alendronate, for up to 10 hours. As noted
35 above, a meal was allowed 4 hours after the administration of alendronate.

In the first (reference) study session, the predose of alfacalcidol and the therapeutic dose of alendronate were administered simultaneously, with 10-20 ml tap

water to facilitate swallowing, immediately followed by 250 ml tap water *via* a gastroesophageal tube.

In the second through fifth study sessions, the predose of alfacalcidol was administered with 10-20 ml tap water. At intervals of 1, 2, 3, or 6 hours, respectively,
 5 following the administration of the predose of alfacalcidol in each of the consecutive study sessions, the therapeutic dose of alendronate was administered with 10-20 ml tap water, immediately followed by 250 ml tap water *via* gastroesophageal tube.

For each alfacalcidol predose time interval tested, cumulative levels of alendronate concentrations in urine were determined over 24 hours post-
 10 administration of the therapeutic alendronate dose at collection time points beginning at the 0 hour prior to alendronate dose and again at 3, 6, 9, and 24 hours following the alendronate dose.

The results of the analyses of alendronate in urine for the five treatments are reported in Tables 1A–1E, 2 and 3. Tables 1A–1E give the results of the excretion of
 15 alendronate into dog urine for each of the experimental sessions. Table 2 collects the average of the total excreted alendronate as a function of the time interval between alfacalcidol administration and alendronate administration. Table 3 gives the average of total excreted alendronate as a function of the time interval between calcitriol administration and alendronate administration carried out in a separate experiment.

20 The results showed that the total alendronate bioavailability increased considerably 6 hours after the administration of alfacalcidol. It is expected that this increase will continue to be found when the time interval between administration of the predose of alfacalcidol and the subsequent administration of the therapeutic dose of alendronate is increased to 8, 10 or 12 hours. Alendronate bioavailability without
 25 the vitamin D analogue in this dog model was about 30 µg to 50 µg. Calcitriol, administered 3 hours before the alendronate administration increased this value to 108 µg. The improvement in alendronate bioavailability was similar for the two vitamin D analogues, calcitriol and alfacalcidol, but the optimal time interval between administration of the predose and maximum alendronate bioavailability was delayed
 30 in the case of alfacalcidol. This delay can be used to advantage in designing a combination drug regimen with a dose scheme that is convenient and improves the bioavailability of alendronate.

TABLE 1A (alendronate 0 hours after 1-alpha)**SUMMARY OF ALENDRONATE QUANTITY
EXCRETED (μ g) IN URINE**

Subject #	Period #	Draw Times (Hour)					total
		0.000	3.00	6.00	9.00	24.0	
295	1	BLQ	NRV	6.09	NRV	NRV	6.09
109	1	BLQ	27.33	4.27	BLQ	4.20	35.80
612	1	BLQ	28.01	NRV	NRV	2.91	30.92
648	1	BLQ	40.99	6.90	8.45	7.02	63.36
005	1	BLQ	28.26	8.87	3.52	2.90	43.55
578	1	BLQ	25.29	13.99	2.21	3.68	45.17
						avg=	37.48

BLQ: Below Level of Quantitation

NRV: No Reportable Value

5

TABLE 1B (alendronate 1 hour after 1-alpha)**SUMMARY OF ALENDRONATE QUANTITY
EXCRETED (μ g) IN URINE**

Subject #	Period #	Draw Times (Hour)					total
		0.000	3.00	6.00	9.00	24.0	
295	2	BLQ	42.05	4.71	NRV	7.58	54.34
109	2	BLQ	39.99	4.01	NRV	3.47	47.47
612	2	BLQ	39.73	4.42	4.30	4.58	53.03
648	2	1.61	109.98	9.02	7.51	8.79	136.91
005	2	BLQ	BLQ	BLQ	BLQ	BLQ	0.00
578	2	BLQ	4.87	1.82	NRV	NRV	6.69
						avg=	49.74

BLQ: Below Level of Quantitation

NRV: No Reportable Value

TABLE 1C (alendronate 2 hours after 1-alpha)**SUMMARY OF ALENDRONATE QUANTITY
EXCRETED (μ g) IN URINE**

Subject #	Period #	Draw Times (Hour)					total
		0.000	3.00	6.00	9.00	24.0	
295	3	3.14	25.52	NRV	3.82	5.84	38.32
109	3	BLQ	NRV	NRV	2.30	2.97	5.27
612	3	BLQ	NRV	4.11	2.73	4.11	10.95
648	3	BLQ	38.98	20.58	7.32	11.28	78.16
005	3	NRV	BLQ	NRV	NRV	NRV	0.00
578	3	BLQ	16.10	9.63	1.80	NRV	27.53
						avg=	26.71

BLQ: Below Level of Quantitation

NRV: No Reportable Value

5

TABLE 1D (alendronate 3 hours after 1-alpha)**SUMMARY OF ALENDRONATE QUANTITY
EXCRETED (μ g) IN URINE**

Subject #	Period #	Draw Times (Hour)					total
		0.000	3.00	6.00	9.00	24.0	
295	4	NRV	59.51	5.68	3.87	3.97	73.03
109	4	BLQ	81.05	7.04	NRV	5.06	93.15
612	4	BLQ	35.52	5.01	NRV	4.12	44.65
648	4	BLQ	47.20	7.05	5.72	NRV	59.97
005	4	BLQ	51.07	11.11	13.24	20.07	95.49
578	4	3.81	85.63	13.41	7.10	6.81	116.76
						avg=	80.51

BLQ: Below Level of Quantitation

NRV: No Reportable Value

TABLE 1E (alendronate 6 hours after 1-alpha)**SUMMARY OF ALENDRONATE QUANTITY
EXCRETED (μ g) IN URINE**

Subject #	Period #	Draw Times (Hour)					total
		0.000	3.00	6.00	9.00	24.0	
295	5	BLQ	65.02	31.98	6.03	7.28	110.31
109	5	BLQ	49.30	5.09	2.39	4.64	61.42
612	5	4.10	111.68	10.42	4.61	12.55	143.36
648	5	NRV	68.15	8.78	4.25	5.27	86.45
005	5	4.73	65.30	2.55	6.54	5.56	84.68
578	5	NRV	75.32	11.65	3.71	3.67	94.35
						avg=	96.76

BLQ: Below Level of Quantitation

NRV: No Reportable Value

Table 2. Average Total Alendronate Excreted as a Function of the Time Interval
Between Alfacalcidol and Alendronate Administrations

Hours between administrations	total alendronate (μ g)
0	37.5
1	49.7
2	26.7
3	80.5
6	96.8

Table 3. Average Total Alendronate Excreted as a Function of the Time Interval
Between Calcitriol and Alendronate Administrations

Hours between administrations	total alendronate (μ g)
0	56.9
1	56.8
2	70.0
3	108.1
6	36.0

ABSTRACT

The present invention provides a method of combination drug therapy that includes the steps of administering a separate predose of a vitamin D analogue which is
5 a calcium transport stimulator, especially alfacalcidol, followed by administration of a therapeutic dose of a bisphosphonate, especially alendronate, that improves the bioavailability of the bisphosphonate, wherein the predose of the vitamin D analogue is administered at least about six hours before the therapeutic dose of the bisphosphonate is administered.

EXHIBIT K

CLOCK COPYIN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,

Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

C.A. No. 01-0048 (JJF)
(CONSOLIDATED)**FILED**
CLERK U.S. DISTRICT COURT
DISTRICT OF DELAWARE
2003 APR 11 PM 4:35**MERCK'S MOTION TO ADD TEVA'S U.S. PATENT NO. 6,476,006
TO THE RECORD AS PLAINTIFF'S TRIAL EXHIBIT 301**

Plaintiff Merck & Co., Inc. ("Merck") hereby moves to add to its trial exhibit list U.S. Patent No. 6,476,006 (the "'006 patent") entitled "Composition and Dosage Form for Delayed Gastric Release of Alendronate and/or Other Bisphosphonates," attached as Exhibit A which Teva should have produced, but failed to, in discovery. The original application for the '006 patent was filed in June 2000, by Teva Pharmaceutical Industries, Ltd. ("Teva Limited") and the patent issued on November 5, 2002. Teva Limited is the parent company of Teva and its representatives were present at the trial (Trial Transcript 3:3-9 (Galbraith)).

Merck discovered this highly probative patent just a week ago in connection with responding to new contentions of Teva. Specifically, at page 47 of its opening post-trial brief, served March 28, 2003, Teva now argues that the commercial success of once-weekly FOSAMAX[®] is not relevant to this case since "no one else had the incentive to develop new dosing forms of alendronate because no one else could bring an improved dosage form to

market” before September 2000.¹ But the '006 patent reveals that Teva itself must have been developing new dosage forms for alendronate in Israel well before 2000.

Teva's '006 patent is also at odds with Teva's attack on the evidence introduced at trial that, in July 1997, skilled professionals would have expected that high unit doses of alendronate sodium would exacerbate the gastrointestinal side effects caused by the drug. Teva even argued that this expectation was inconsistent with the facts and the science. *See* Teva's Post-Trial Brief, at pp. 1, 27-28. Yet, Teva had adopted and advanced Merck's view in the '006 patent while seeking the allowance of its own claims relating to a delayed gastric release dosage form for alendronate. Specifically, Teva told the PTO that:

Bis-phosphonates such as alendronate, residronate, etidronate and teludronate are commonly prescribed drugs Despite their benefits, bis-phosphonates suffer from ... side effects that consist of irritation of the upper gastrointestinal mucosa [citing “Esophagitis and Alendronate”]. ... Since bisphosphonates are not metabolized, dosing [frequency] could be lowered to once a week instead of daily (70 mg per dose once a week in place of 10 mg per dose daily) [citing the '329 patent]. ***While large dosing helps improve patient compliance, it has the potential of exacerbating the upper GI side effects of the drug.***

Exhibit A, at col. 3, ll. 34-42 (emphasis added).

Despite the '006 patent's relevance to this case, Teva never produced it. This was improper especially since Teva's trial counsel, Kenyon & Kenyon, prosecuted the '006 patent for Teva before the PTO (*see* Exhibit A).

While responding to Teva's new argument that purportedly no one else had an incentive to develop new alendronate dosage forms, last week, Merck discovered the '006 patent, showing that Teva itself had been developing new dosage forms of alendronate since before 2000. The

¹ Teva never raised the argument that no one else had an incentive to develop new alendronate dosing forms in its responses to Merck's interrogatories, in its economist's, Dr. Rozek's, expert report, or in the Pre-Trial Order. Teva mentioned it in passing during its opening statement at trial, but cited no evidence and adduced none at trial.

'006 patent was responsive to several Merck document requests, including Nos. 2, 13, 16, 31, 34, and 49, yet Teva never produced it. *See* Exhibit B, Merck's First Set of Document Requests. In this litigation, Merck questioned Teva's counsel several times about Teva's meager document production, and even filed a Motion to Compel Production (D.I. 95). Merck eventually agreed to withdraw its Motion to Compel only after Teva gave its assurances that it had conducted diligent searches, and that all responsive documents had been produced. *See, e.g.*, Exhibit C, October 9, 2002 letter from Danae Schuster to Scott Garber; and Exhibit D, December 11, 2002, letter from Maria Palmese to Nicolas Barzoukas.

That the '006 patent was filed by Teva's parent company, Teva Limited, does not relieve Teva of its obligation to have produced the '006 patent. First, Merck specifically requested documents of not only Teva USA, but also relevant documents from its parent. *See* Exh. B, Merck's First Set of Document Requests, at p. 4. ¶ I. Second, Teva had an obligation to produce the '006 patent and its file history, because both Teva and Kenyon & Kenyon had access to and control of these documents, they were highly relevant to the very issues Teva raised in this case, and they were well within its ability to obtain. In fact they were in Kenyon & Kenyon's files. *See Camden Iron and Metal, Inc. v. Marubeni America Corp.*, 138 F.R.D. 438, 443-44 (D.N.J. 1991) (Ordering defendant to produce documents held by its parent corporation because, among other things, the defendant "has easy and customary access to the [parent's] documents . . . [and] possesses the ability to obtain such documents . . . for its usual business needs. ***One such business need is to provide highly relevant documents in litigation.***") (emphasis added); *Cooper Indus., Inc. v. British Aerospace*, 102 F.R.D. 918, 919-20 (S.D.N.Y. 1984) (Granting Plaintiff's motion to compel documents and for sanctions when Defendant refused to produce available documents held by its foreign affiliate.) Here, not only Teva had access to this alendronate-

related patent and application in connection with its business (as Teva, by this lawsuit, is seeking to be in the alendronate business), but these documents were in its trial counsel's office.

For these reasons, Merck submits that the Court should grant Merck's motion and add Teva's U.S. Patent No. 6,476,006, entitled "Composition and Dosage Form for Delayed Gastric Release of Alendronate and/or Other Bisphosphonates," to the trial record as Plaintiff's Trial Exhibit 301.

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EXHIBIT A



US006476006B2

(12) **United States Patent**
Flashner-Barak et al.

(10) **Patent No.:** **US 6,476,006 B2**
(45) **Date of Patent:** **Nov. 5, 2002**

(54) **COMPOSITION AND DOSAGE FORM FOR DELAYED GASTRIC RELEASE OF ALENDRONATE AND/OR OTHER BIS-PHOSPHONATES**

(75) Inventors: **Moshe Flashner-Barak**, Petach Tikva (IL); **Vered Rosenberger**, Jerusalem (IL); **Mazal Dahan**, Jerusalem (IL); **Yitzhak Lerner**, Petach Tikva (IL)

(73) Assignee: **Teva Pharmaceutical Industries, Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/770,898**

(22) Filed: **Jan. 26, 2001**

(65) **Prior Publication Data**

US 2002/0015733 A1 Feb. 7, 2002

Related U.S. Application Data

(60) Provisional application No. 60/260,438, filed on Jan. 9, 2001, and provisional application No. 60/213,832, filed on Jun. 23, 2000.

(51) Int. Cl.⁷ **A01N 57/26**; **A61K 31/66**

(52) U.S. Cl. **514/76**; **514/102**; **514/106**; **514/109**

(58) Field of Search **424/484**; **514/102**, **514/106**, **109**, **76**

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(57) **ABSTRACT**

The present invention provides compacted pharmaceutical composition for oral administration to a patient which expands upon contact with gastric fluid to retain a dosage form in the patient's stomach for an extended period of time, the formulation comprising a non-hydrated hydrogel, a superdisintegrant and tannic acid. The present invention further provides a pharmaceutical dosage form containing an active ingredient, and the compacted pharmaceutical composition. The invention further provides a dosage form suitable for delivering a therapeutic bis-phosphonate such as alendronate to the stomach of a patient over and extended period.

42 Claims, No Drawings

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COMPOSITION AND DOSAGE FORM FOR DELAYED GASTRIC RELEASE OF ALENDRONATE AND/OR OTHER BIS- PHOSPHONATES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 (e) of U.S. provisional applications Ser. No. 60/213,832, filed Jun. 23, 2000 and Ser. No. 60/260,438, filed Jan. 9, 2001, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to gastric retention systems and to pharmaceutical dosage forms that use them to release a drug in a patient's stomach or duodenum. More particularly, the invention relates to gastric retention systems suitable for use with bis-phosphonates such as alendronic acid and its pharmaceutically acceptable salts and hydrates thereof, to release these drugs in a controlled manner.

BACKGROUND OF THE INVENTION

After discovery of a new drug for treatment of a human disease further investigation must be undertaken to determine whether it is most effective to administer the drug to a patient intravenously, transdermally, subcutaneously or orally. Orally administered drugs are easy to administer and therefore are often favored whenever an oral route is feasible. However, compliance problems sometimes occur with orally administered drugs when the dosage form is inconvenient to take or must be taken frequently or at inconvenient times. Orally administered drugs are often presented to a patient in such dosage forms as tablets, pills, lozenges and capsules. Most orally administered drugs are absorbed into the bloodstream from the patient's gastrointestinal tract, excepting inhalants which are absorbed by the lungs and sinuses.

Orally-administered drug may be absorbed more readily by the gastrointestinal ("GI") tract through either the stomach wall or the intestine wall. Few drugs are efficiently absorbed by the colon. Tablets that are designed to carry drugs that are more readily absorbed through the intestine wall are sometimes covered with a coating that is resistant to the acidic conditions of the stomach but which decomposes under the basic conditions of the intestine. This enteric coating allows the tablet to transit the stomach without releasing the active ingredient until it reaches the portion of the GI tract where it is most readily absorbed. This enteric-coating strategy is also effective when the drug is caustic to the lining of the stomach or decomposes under acidic conditions.

It is sometimes desirable that a drug be released in a patient's stomach rather than in the intestine. One such instance is when it is therapeutically advantageous to release the drug over several hours. The average residence time of solid food in the small intestine is about three hours. A controlled release pharmaceutical dosage form may pass through the stomach and intestine and into the colon before the active ingredient has been completely released. However, if the dosage form is retained in the stomach, complete release occurs upstream of the small intestine and the active ingredient will enter the intestine in an unbound state in which it can be readily absorbed before reaching the colon.

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It is also desirable to release a drug in the stomach when it is unstable to the basic conditions of the intestine. A composition that is formulated to dissolve upon contact with any aqueous solution will at least partially dissolve in the stomach because it reaches the stomach before it reaches the intestine. However, the average residence time of food in the stomach is only about 1 to 3 hours. Unless the drug is very rapidly absorbed, or the residence time is increased, some of the drug will pass to the intestine. An unstable drug will at least partially decompose to a product compound that either is not absorbed or, if absorbed, may not exert the desired therapeutic effect. Accordingly, decomposition of a base sensitive drug that passes into the intestine reduces the effectiveness of the dosage and, as well, introduces an uncontrollable factor that is detrimental to accurate dosing.

For the foregoing reasons, formulation chemists have developed strategies to increase the retention time of oral dosages in the stomach. One of the general strategies, involves using an intragastric expanding dosage form that swells upon contact with stomach juices, preventing its passage through the pylorus. Intragastric expanding dosage forms use hydrogels which expand upon contact with water to expand the dosage form to sufficient size to prevent its passage through the pylorus. An example of such a dosage form is described in U.S. Pat. No. 4,434,153. The '153 patent discloses a device for executing a therapeutic program after oral ingestion, the device having a matrix formed of a non-hydrated hydrogel and a plurality of tiny pills containing a drug dispersed throughout the matrix.

As reviewed by Hwang, S. et al. "Gastric Retentive Drug-Delivery Systems," *Critical Reviews in Therapeutic Drug Carrier Systems*, 1998, 15, 243-284, one of the major problems with intragastric expanding hydrogels is that it can take several hours for the hydrogel to become fully hydrated and to swell to sufficient size to obstruct passage through the pylorus. Since food remains in the stomach on average from about 1 to 3 hours, there is a high probability that known expanding dosage forms like that of the '153 patent will pass through the pylorus before attaining a sufficient size to obstruct passage.

The rate-limiting factor in the expansion of ordinary hydrogels is the rate of delivery of water to non-surficial hydrogel material in the dosage form. Conventional non-hydrated hydrogels are not very porous when dry and ingress of water into the hydrogel is slowed further by the formation of a low permeability gelatinous layer on the surface after initial contact with water. One approach to solving this problem uses so-called superporous hydrogels. Superporous hydrogels have networks of pores of 100 μ diameter or more. Pores of that diameter are capable of efficient water transport by capillary action. Water reaches the non-surficial hydrogel material quickly resulting in a rapid expansion of the superporous hydrogel to its full extent. However, there are also shortcomings attendant to the use of superporous hydrogels. They tend to be structurally weak and some are unable to withstand the mechanical stresses of the natural contractions that propel food out of the stomach and into the intestine. The superporous hydrogels tend to break up into particles too small to be retained.

Non-superporous hydrogels do not suffer from mechanical strength problems to as great an extent as superporous hydrogels. An additional advantage of using conventional hydrogels is that their degradation/erosion rates are well studied. The blended composition of the present invention should be compared with the superporous hydrogels described in Chen, J. and Park, K. *Journal of Controlled Release* 2000, 65, 73-82, wherein the mechanical strength

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of superporous hydrogels is improved by the polymerization of precursor hydrogel monomers in the presence of several superdisintegrants. The result of the polymerization described by Chen and Park is a new substance having interconnecting cross-linking networks of polyacrylate and, e.g. cross-linked carboxymethyl cellulose sodium. Such interconnecting networks are not expected to have the same degradation rates as conventional hydrogels made from the same precursor hydrogel monomers.

Many disease therapies can benefit from improvements in controlled gastric release technology, such as osteoporosis and Paget's disease. Bis-phosphonates such as alendronate, residronate, etidronate and teludronate are commonly prescribed drugs for treatment of these diseases. Despite their benefits, bis-phosphonates suffer from very poor oral bioavailability (Gert, B. J.; Holland, S. D.; Kline, W. F.; Matuszewski, B. K.; Freeman, A.; Quan, H.; Lasseter, K. C.; Mucklow, J. C.; Porras, A. G.; Studies of the oral bioavailability of alendronate, *Clinical Pharmacology & Therapeutics* (1995) 58, 288-298), serious interference of absorption by foods and beverages other than water (ibid.), and side effects that consist of irritation of the upper gastrointestinal mucosa (Lieberman, U. A.; Hirsch, L. J.; Esophagitis and alendronate, *N. Engl. J. Med.* (1996) 335, 1069-70) with the potential for this irritation leading to more serious conditions (Physicians' Desk Reference, Fosamax, Warnings).

To overcome these limitations, the bis-phosphonates, such as alendronate, are given in relatively large doses in a fasting condition while maintaining an upright position for at least a half an hour after dosing (Physicians' Desk Reference, Fosamax, Dosage and Administration). The standard treatment with the bis-phosphonates is chronic and daily, so the inconvenience to the patient can lead to non compliance with the dosage regimen. Since bis-phosphonates are not metabolized, dosing could be lowered to once a week instead of daily (70 mg per dose once a week in place of 10 mg per dose daily) by administering very large sustained-release doses of the drug, (Daifotis, A. G.; Santora II, A. C.; Yates, A. G.; Methods for inhibiting bone resorption, U.S. Pat. No. 5,994,329). While large dosing helps improve patient compliance, it has the potential of exacerbating the upper GI side effects of the drug.

Alendronate is best absorbed from the upper GI tract (duodenum and jejunum) (Lin, J. H.; Bisphosphonates: a review of their pharmacokinetic properties, *Bone* (1996), 18, 75-85. Porras, A. G.; Holland, S. D.; Gertz, B. J.; Pharmacokinetics of Alendronate, *Clin Pharmacokinet* (1999) 36, 315-328), and is better absorbed at a pH of ~6 (Gert, B. J.; Holland, S. D.; Kline, W. F.; Matuszewski, B. K.; Freeman, A.; Quan, H.; Lasseter, K. C.; Mucklow, J. C.; Porras, A. G.; Studies of the oral bioavailability of alendronate, *Clinical Pharmacology & Therapeutics* (1995) 58, 288-298). Only gastric retention with controlled release allows for the extended delivery of a drug to the duodenum. Controlled release of the drug to the duodenum and jejunum parts of the intestine should allow an improvement in bioavailability, thus allowing a lowering of the total dose of the drug.

SUMMARY OF THE INVENTION

We have now found a rapidly expanding oral dosage form that swells rapidly in the gastric juices of a patient, thereby increasing the likelihood that an active ingredient carried by the form will be released in the stomach. This oral design form employs a blend of a superdisintegrant, tannic acid and one or more conventional hydrogels. The dosage forms of the present invention swell rapidly, yet because they do not

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require superporous hydrogels, do not have their associated mechanical strength problems.

The present invention further provides compacted pharmaceutical compositions for oral administration to a patient which expand upon contact with gastric fluid to retain a dosage form in the patient's stomach for an extended period of time, the formulation comprising a blend of a non-hydrated hydrogel, a superdisintegrant and tannic acid.

The present invention further provides a pharmaceutical dosage form containing an active ingredient and the compacted pharmaceutical composition.

Yet further, the present invention provides compositions and dosage forms for delayed release of bis-phosphonates. The dosage forms release the bis-phosphonates into the stomach of a patient suffering from osteoporosis or Paget's disease. The dosage forms include a drug delivery vehicle which retains the dosage form in the patient's stomach for an extended period of time. In some embodiments of the invention, the drug delivery vehicle further provides a means to slow the release of the bis-phosphonate. Bis-phosphonate is released into the stomach over at least a portion of the period that the dosage form is retained in the stomach.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a carrier composition for a pharmaceutically active ingredient and dosage forms containing the carrier composition and the active ingredient. Tablets containing the inventive composition swell rapidly on contact with aqueous solution, such as the gastric juices of a patient and simulated gastric fluid. Rapid swelling is achieved by a novel combination of hydrogel, superdisintegrant and tannic acid.

The preferred hydrogel of the present invention is hydroxypropylmethylcellulose, either alone or in combination with hydroxypropyl cellulose and/or a cross-linked acrylate polymer. Suitable cross-linked acrylate polymers include polyacrylic acid crosslinked with allyl sucrose commercially available under the trade name Carbopol® (BF Goodrich Chemical Ltd.) and polyacrylic acid cross linked with divinyl glycol. As further illustrated by Examples 5 and 8, below, a preferred hydrogel of the invention is a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose. The most preferred hydrogel of the present invention is a combination of hydroxypropyl methylcellulose and hydroxypropyl cellulose in a weight ratio of from about 1:3 to about 5:3. The molecular weight of the hydrogels is not critical to practice of the invention.

The inventive composition also includes a superdisintegrant. Superdisintegrants are pharmaceutical excipients within a larger class of excipients known as disintegrants. Disintegrants are typically hydrophilic polymers of either natural or synthetic origin. Superdisintegrants are disintegrants that swell upon contact with water. Preferred superdisintegrants of the present invention swell to at least double their non-hydrated volume on contact with water. Exemplary of these superdisintegrants are cross-linked polyvinyl pyrrolidone (a.k.a. crospovidone), cross-linked carboxymethyl cellulose sodium (a.k.a. croscarmellose sodium) and sodium starch glycolate. Crospovidone is commercially available from BASF Corp. under the tradename Kollidon® CL and from International Specialty Chemicals Corp. under the tradename Polyplasdone®. Croscarmellose sodium is commercially available from FMC Corp. under the tradename Ac-Di-Sol® and from Avebe Corp. under the trade-

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name Primellose®. Sodium starch glycolate is commercially available from Penwest Pharmaceuticals Co. under the tradename Explotab® and from Avebe Corp. under the tradename Primojel®. The most preferred superdisintegrant is sodium starch glycolate.

The inventive composition further includes tannic acid. Tannic acid, also called tannin, gallotannin and gallotannic acid, is a naturally occurring constituent of the bark and fruit of many trees. The term "tannins" conventionally refers to two groups of compounds, "condensed tannins" and "hydrolyzable tannins." *Merck Index* monograph No. 8828 (9th ed. 1976). The hydrolyzable tannins are sugars that are esterified with one or more (polyhydroxylarene) formic acids. One common polyhydroxylarene formic acid is galloyl (i.e. 3,4,5-trihydroxybenzoyl). Another common polyhydroxylarene formic acid substituent of tannins is meta-digallic acid. A common sugar moiety of tannins is glucose. The tannic acid of the present invention is selected from the hydrolyzable tannins, and especially glucose tannins in which one or more of the hydroxyl groups of glucose is esterified with gallic acid and/or meta-digallic acid.

The novel expanding composition of the present invention comprises hydroxypropyl methylcellulose, optionally in combination with other hydrogel polymers, a superdisintegrant and tannic acid. These excipients are preferably combined in a weight ratio, exclusive of any other excipients that may be present, of from about 20 wt. % to about 80 wt. % hydrogel, from about 10 wt. % to about 75 wt. % superdisintegrant and from about 2 wt. % to about 15 wt. % tannic acid. A preferred composition comprises from about 30 wt. % to about 55 wt. % superdisintegrant, about 5 wt. % (± 2 wt. %) tannic acid, plus an amount of hydrogel sufficient to bring the total to 100 wt. %.

One especially preferred embodiment of the present invention is a rapidly expanding pharmaceutical composition comprising from about 10 wt. % to about 20 wt. % hydroxypropyl methyl cellulose, from about 45 wt. % to about 50 wt. % hydroxypropyl cellulose, about 25 wt. % to about 35 wt. % sodium starch glycolate and about 4 wt. % to about 6 wt. % tannic acid. A second especially preferred embodiment of the present invention is a rapidly expanding pharmaceutical composition comprising from about 20 wt. % to about 30 wt. % hydroxypropyl methyl cellulose, from about 10 wt. % to about 20 wt. % hydroxypropyl cellulose, about 45 wt. % to about 55 wt. % sodium starch glycolate and about 4 wt. % to about 6 wt. % tannic acid.

The novel composition of the invention can be prepared conventionally by dry blending. In order to form a structurally resilient mass upon contact with water or gastric fluid, the blended composition is compacted prior to hydration.

One object of the invention is to provide a dosage form such as a tablet that is retained in the stomach for an extended period of time by swelling to a size that prevents passage through the pylorus upon contact with gastric juices. Over time the swollen tablet degrades or erodes into particles that are sufficiently small to traverse the pylorus. The tablet may be compacted following conventional dry granulation or direct compression techniques.

The pharmaceutical dosage forms of the present invention comprise the compacted expanding composition of the invention and an active ingredient. Active ingredients that may be carried by these dosage forms include, but are in no way limited to, bis-phosphonates such as alendronic acid and its pharmaceutically acceptable salts and hydrates, levodopa, carbidopa, methylphenidate, diltiazem, irinotecan and etoposide. Preferably, the pharmaceutical dosage forms

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are retained in the stomach for three hours or more, more preferably about five hours or more. In order to obstruct passage through the pylorus, the dosage form preferably swells by a factor of five or more, more preferably about eight or more, within about fifteen minutes of contacting gastric fluid. Yet more preferably, such swelling is reached within about five minutes.

The novel composition of the invention can be prepared conventionally by dry blending. In order to form a structurally resilient mass upon contact with water or gastric fluid, the blended composition is compacted prior to hydration. The composition may be compacted following conventional dry granulation or direct compression techniques.

For instance, the blended composition may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may be compressed subsequently into a final dosage form. It will be appreciated that the processes of slugging or roller compaction, followed by comminution and recompression render the hydrogel, superdisintegrant and tannic acid intragranular in the final dosage form. The active ingredient of the pharmaceutical may also be provided intragranularly by blending it with the expanding composition prior to compaction. Alternatively the active ingredient may be added after comminution of the compacted composition, which results in the active ingredient being extragranular.

As an alternative to dry granulation, the blended composition may be compressed directly into the final pharmaceutical dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Thus the active ingredient and any other desired excipients are blended with the composition prior to direct compression tableting. Such additional excipients that are particularly well suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. An additional alternative to dry granulation is wet granulation. The blend of excipients may be granulated using water or an alcohol as a granulation solvent by standard granulation techniques known in the art followed by drying.

In addition to the above-described excipients, the rapidly expanding pharmaceutical composition and dosage form may further include any other excipients. One factor that must be taken into account in formulating a pharmaceutical composition is the mechanical process which the composition undergoes to be transformed into a dosage form, such as a tablet or capsule. Some excipients are added to facilitate this mechanical processing, such as glidants and tablet lubricants. Glidants improve the flow properties of the composition in powder or granule form while lubricants ease ejection of a tablet from the tableting dye in which it is formed by compression. Silicon dioxide is a common glidant, while magnesium is a common tablet lubricant. Thus, for example, the present inventive composition may further include silicon dioxide and magnesium stearate. Other excipients which may be mentioned are binders, that are added to prevent flaking and other types of physical disintegration of the tablet prior to ingestion by a patient. Yet other excipients are diluents whose presence causes the tablet to be larger and thus easier for a patient to handle.

Further increase in retention times can be realized by the addition of a compound that produces gas when contacted with acid, such as sodium bicarbonate. Sodium bicarbonate may be provided by blending into the expanding composition of the invention or may be an extragranular constituent of a tablet prepared by dry granulation. Sodium bicarbonate

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is preferably used at low concentration, of from about 0.5 wt. % to about 5 wt. % of expanding composition.

In addition to the above-described use of the expanding composition in tablets prepared by dry or wet granulation and compression, there are many other embodiments in which the expanding composition could be used to retain a drug delivery vehicle in the stomach. For instance, the expanding composition can be used to coat a smaller tablet (this is a preferred construction of a gastric retention dosage form of alendronate, described below). The expanding composition can be used advantageously in this way in sustained delivery of a drug. After contact with aqueous fluid and swelling, the composition is highly porous. Thus, the release rate of a sustained release dosage form like a coated tablet or slowly desintegrating tablet is substantially unaffected by a coating of the expanding composition.

The expanding composition is also suited for the retention of drugs in the stomach when such drugs are contained in tablets that are either partially embedded in the expanding composition or attached thereto by an adhesive. These tablets can be of a slow release nature giving slow or controlled release for an extended period of time in the stomach. These tablets can further be of a delayed pulse release nature. The expanding composition of this invention will retain these forms in the stomach until the delay time has passed whereupon the drug will be released in a burst or pulse fashion. Attaching, or partially embedding, several such tablets, each timed with a different delay to release, to the composition of this invention, allows versatile dosing schemes from one taken dose. For example, one could deliver three (or more) timed doses in a pulse fashion while the patient needs to take the dose only once. The three doses would mimic taking three doses of the drug at the prescribed times, with the drug being absorbed from the stomach with each dose. Such dosing allows for improved compliance to dosage schedules and in many cases will lead thereby to improved therapy.

Delayed dosage forms that are not coupled to gastric retention will deliver each such dose in a different part of the GI tract with different absorption profiles for each of the doses. Such therapy would not be equivalent to taking three doses of the drug at the prescribed times, wherein the drug would have been absorbed from the stomach in each case.

The present invention provides a delayed release dosage form containing the delivery vehicle/composition of the invention and a therapeutic bis-phosphonate that is capable of delivering the bis-phosphonate to the stomach of a patient several hours after administration.

Suitable bis-phosphonates include alendronic acid and its pharmaceutically acceptable salts and hydrates thereof, as well as residronate, etidronate and teludronate.

The bis-phosphonate drug delivery vehicle may be formed from the afore-described hydrogel, superdisintegrant and tannic acid by blending or granulating. Regardless of the method by which the hydrogel, superdisintegrant and tannic acid are combined, they are preferably combined in a weight ratio, exclusive of the bis-phosphonate and any other excipients that may be present, of from about 50 wt. % to about 80 wt. % hydrogel, from about 10 wt. % to about 30 wt. % superdisintegrant and from about 5 wt. % to about 15 wt. % tannic acid. A yet more preferred drug delivery vehicle comprises from about 15 wt. % to about 25 wt. % superdisintegrant, about 10 wt. % (± 2 wt. %) tannic acid, plus an amount of hydrogel sufficient to bring the total to 100 wt. %. One especially preferred bis-phosphonate delivery vehicle comprises from about 15 wt. % to about 20 wt. %

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% hydroxypropyl methyl cellulose, from about 45 wt. % to about 55 wt. % hydroxypropyl cellulose, about 20 wt. % to about 25 wt. % carboxy methyl cellulose sodium and about 8 wt. % to about 12 wt. % tannic acid.

Dosage forms containing the drug delivery vehicle and bis-phosphonate swell rapidly on contact with aqueous solution, e.g. water, gastric fluid and acidic solutions like simulated gastric fluid. In order to obstruct passage through the pylorus, the drug delivery vehicle preferably swells by a factor of five or more, more preferably about eight or more, within about fifteen minutes of contacting gastric fluid. Yet more preferably, such swelling is reached within about five minutes. Preferably, the swelling causes retention of the pharmaceutical dosage forms in the stomach for three hours or more, more preferably about four hours or more, after which time the drug delivery vehicle either dissolves or degrades into fragments small enough to pass through the pylorus.

The invention further relates to specific pharmaceutical dosage forms containing a therapeutic bis-phosphonate and the drug delivery vehicle. These forms may have (a) a monolithic construction, such as a tablet made by conventional direct compression or granulation techniques wherein the active is dispersed in the drug delivery vehicle, (b) a layered construction wherein the active, alone or in mixture with any other excipients, form a layer that is bonded, e.g. by compression, to another layer formed of the drug delivery vehicle, (c) an encapsulated construction wherein either of the (a) or (b) type constructions are encapsulated, (d) a coated construction wherein a core containing the actives is coated with the drug delivery vehicle, and (e) a construction whereby the drug is incorporated in an optionally coated matrix tablet, said tablet being partially embedded in the drug delivery vehicle, or attached externally to the drug delivery vehicle by an adhesive.

A monolithic dosage form can be prepared by the direct compression and granulation methods previously described. The monolithic dosage form may be made in any shape desired, but it has been found that an ovoid or elliptical shape is advantageous for retaining the dosage form in the stomach. An ovoid or elliptical dosage form preferably is sized at between about 4 mm and 8 mm in two dimensions and between about 10 mm and 20 mm in the third dimension, more preferably about 6x6x16 mm. Monolithic dosage forms slow the release of the actives due to the diffusional barrier created by the surrounding swelled hydrogel. The diffusion may slow to the point that release occurs by erosion of the drug delivery vehicle.

In a monolithic dosage form, delayed release of the actives may be provided by coating the actives with a delay release coating according to methods known to the art. Thus, where the foregoing description of the present invention has described mixing, blending, granulating, compressing, etc. of the actives, it will be appreciated by those skilled in the art that the actives may previously be coated with a coating that erodes slowly in gastric fluid to provide a delay in release of the actives. In particular, a monolithic dosage form may contain microgranules, microcapsules or coated beads containing the actives.

A particularly preferred bis-phosphonate dosage form is a coated construction wherein the drug delivery vehicle coats a core containing the active. This construction is illustrated in detail with Examples 9-12, below. A coated construction delays the release of the active by providing a diffusional barrier through which the active must pass before it is released. As illustrated in the Examples, a coated construc-

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tion can provide either a delayed/rapid release or a delayed/extended release of the active depending upon the formulation of the core.

A preferred layered construction is one which contains the drug delivery vehicle in one layer and the actives in another layer. Preferred dimensions for this embodiment are about 14x8 mm. A layered construction may be prepared by conventional multilayer compression techniques. A layered dosage form comprising two layers, one comprising the drug delivery vehicle and the other comprising the actives and any other desired excipients, may be made to delay release of the actives by coating only the actives-containing layer with a conventional coating resistant to gastric fluids. A further method of achieving a delay in the release is to formulate the drug containing layer as a matrix that delays diffusion and erosion or by incorporating the active substances in microcapsules or coated beads within the drug containing layer.

The drug delivery vehicle is also suited for the retention of the actives in the stomach when the actives are contained in tablets that are either partially embedded in the drug delivery vehicle or attached thereto by an adhesive. In addition to being of sustained release nature, these tablets can further be of a delayed pulse release nature or a delayed sustained release nature. The expanding composition of this invention will retain these forms in the stomach until the delay time has passed whereupon the drug will be released in a burst or pulse fashion or in a sustained fashion. Attaching, or partially embedding, several such tablets, each timed with a different delay to release, to the composition of this invention, allows versatile dosing schemes from one taken dose. For example, one could deliver three (or more) timed doses in a pulse fashion while the patient needs to take the dose only once. The three doses would mimic taking three doses of the drug at the prescribed times, with the drug

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Having thus described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification and examples. It is intended that the specification, including the examples, is considered exemplary only, with the scope and spirit of the invention being indicated by the claims which follow.

EXAMPLES

Examples 1-8

Materials

The HPMC used was HPMC K-15PM. The hydroxypropyl cellulose used was Klucel® HF NF, available from Hercules. The sodium croscarmellose used was Ac-Di-Sol® obtained from Avebe Corp. The crosslinked polyacrylic acid was Carbopol® 974P obtained from B.F. Goodrich Chemical Ltd. All materials were of pharmaceutical grade.

Preparation of Tablets

The compositions of each of the tablets are summarized in Table 1. All the compositions contain hydroxypropyl methyl cellulose, tannic acid, a superdisintegrant and 1% magnesium stearate. All of the excipients, except for magnesium stearate, were mixed simultaneously and thoroughly blended by hand. Magnesium stearate was then added at a level of 1% w/w and the blend was further mixed by hand until the magnesium stearate was uniformly distributed throughout the composition. The amount of each composition needed to produce a 5 mm thick tablet was determined and then that amount was compressed into 5 mm thick tablets on a Manesty f3 single punch tableting machine with a 10 mm diameter punch and die. Tablets ranged in weight from 350-400 mg and each had a hardness within the range of 5-7 KP as tested in an Erweka hardness tester.

TABLE 1

Excipient	Example No. (wt. %)							
	1	2	3	4	5	6	7	8
hydroxypropyl methylcellulose	23.8	32.7	30.3	23.8	26.7	38.5	34.8	15.9
Hydroxypropyl cellulose cross-linked	0.0	0.0	0.0	0.0	16.0	19.2	0.0	47.6
polyacrylic acid	0	0.0	0.0	0.0	0.0	0.0	8.7	0.0
Total Hydrogel	23.8%	32.7%	30.3%	23.8%	42.7%	57.7%	43.5%	63.5%
Sodium starch glycolate	71.4	65.4	60.6	0.0	53.3	38.5	52.2	31.7
Sodium Croscarmellose	0.0	0.0	0.0	71.4	0.0	0.0	0.0	0.0
Tannic Acid	4.8	2.0	9.1	4.8	4.0	3.8	4.3	4.8
	100%	100%	100%	100%	100%	100%	100%	100%

being absorbed from the stomach with each dose. Such dosing allows for improved compliance to dosage schedules and in many cases will lead thereby to improved therapy. Delayed dosage forms that are not coupled to gastric retention will deliver each such dose in a different part of the GI tract with different absorption profiles for each of the doses. Such therapy would not be equivalent to taking three doses of the drug at the prescribed times, wherein the drug would have been absorbed from the stomach in each case.

In addition to the above-described dosage forms, there are many other dosage forms in which the drug delivery vehicle could be used to deliver a therapeutic bis-phosphonate over a sustained period in the stomach.

Swelling tests

The tablets were added to 40 ml of 0.1M HCl contained in a 50 ml beaker and maintained at 37±2° C. The tablets were removed after fifteen minutes with a tweezers and measured with a caliper. Gel strength was assessed qualitatively with the tweezers.

Results

The results of the swelling tests are summarized in Table 2. Swelling of the hydrogel was enhanced using either sodium croscarmellose or sodium starch glycolate. The formulation can optionally and advantageously contain a mixture of two hydrogel polymers demonstrated by the incorporation hydroxypropyl cellulose and carbopol in the

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formulations of Examples 5, 6 and 8. The tablet that expanded the most (36 times in volume) contained tannic acid at 5% with sodium croscarmellose as the disintegrant. The tablet with the second highest expansion (18x) also contained tannic acid at 5% but used sodium starch glycolate. Both of those gels were qualitatively weak compared to those of examples 5-8. The best performing tablets in terms of a high degree of expansion and good mechanical strength are those of Examples 5 and 8, which contained tannic acid at 5 wt. %, used both hydroxypropyl methylcellulose and hydroxypropyl cellulose hydrogel polymers and contained sodium starch glycolate as disintegrant.

TABLE 2

Example No.	Degree of Swelling ^a	Strength
1	18.1	moderate
2	12.7	moderate
3	7.2	moderate
4	36	moderate
5	10.4	strong
6	2	strong
7	4.5	strong
8	9.7	strong

^aratio of hydrated tablet volume to dry tablet volume

Example 9

Sodium alendronate monohydrate was formulated into an immediate release tablet of 5-mm diameter with the composition of Table 3 by mixing the powders and direct compression in a standard rotary tablet press. Tablet hardness was between 7 and 12 kP.

TABLE 3

Component	Weight (mg)
Sodium alendronate monohydrate	11.6 mg ^a
Microcrystalline cellulose	30 mg
Lactose for direct compression	20 mg
Magnesium stearate	0.5 mg

^aequivalent to 10 mg alendronic acid

This tablet was embedded into 800 mg of gastric retention delivery system (GRDS) matrix of formulation of Table 4 formed by dry mixing of the components and compression in a Kilian RUD-20 press coat machine. The outer tablet is of oval shape with dimensions approximately 17x7x9 mm.

TABLE 4

GRDS Component	weight %
HPMC (Methocel ® K-15M)	17
Tannic acid	10
HPC (Klucel ® HF)	50
Crosscarmellose (aci-di-sol ®)	22
Magnesium stearate	1

The tablet was tested in a USP apparatus 2 dissolution tester at 37° C. in 500 ml 0.1N HCl to simulate gastric conditions. The tablet expanded in about 15 minutes to dimensions of 22x10x23 mm, large enough to effect gastric retention since the tablet in its swollen state will not fit through the pylorus. The results of the release of the alendronate are given in Table 5. Essentially no alendronate was released during the first three hours. The drug was then released at a relatively fast rate from the disintegrating inner tablet through the GRDS matrix.

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TABLE 5

Time (h)	Cumulative % release
0	0
1	0
2	0
3	3
4	50
5	100

Example 10

Sodium alendronate monohydrate was formulated into an extended release tablet of 5-mm diameter with a composition shown in Table 6 by mixing the powders and direct compression in a standard rotary tablet press. Tablet hardness was between 7 and 12 kP.

TABLE 6

Component	Weight (mg)
Sodium alendronate monohydrate	11.6 mg ^a
Microcrystalline cellulose	25 mg
Lactose	25 mg
Magnesium stearate	0.5 mg

^aequivalent to 10 mg alendronic acid

This tablet was embedded into 800 mg of Gastric Retention Delivery System (GRDS) matrix of formulation of Table 7 formed by dry mixing of the components and compression in a Kilian RUD-20 press coat machine. The outer tablet is of oval shape with dimensions about 17x7x9 mm.

TABLE 7

Component	weight %
HPMC (Methocel K-15M)	17
Tannic acid	10
HPC (Klucel HF)	50
Crosscarmellose (aci-di-sol)	22
Magnesium stearate	1

The tablet was tested in a USP apparatus 2 dissolution tester at 37° C. in 500 ml 0.1N HCl to simulate gastric conditions. The tablet expanded in 15 minutes to dimensions of 22x10x23 mm, sufficiently large to cause gastric retention. The results of the release of the alendronate are given in Table 8. Essentially no alendronate was released during the first three hours. The drug was then released at a slow extended release profile.

TABLE 8

Time (h)	Cumulative % release
0	0
1	0
2	0
3	2
4	9
5	15
6	21
7	27
8	32
9	36

Example 11

Sodium alendronate monohydrate (11.6 mg) was formulated into a tablet of 5-mm diameter with 50 mg of the

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GRDS composition shown in Table 7 above by mixing the powders and direct compression in a standard rotary tablet press. Tablet hardness was between 7 and 12 kP. This tablet is embedded into 800 mg of Gastric Retention Delivery System (GRDS) matrix formulation of Table X formed by dry mixing of the components and compression in a Kilian RUD-20 press coat machine. The outer tablet was of oval shape with dimensions about 17×7×9 mm.

The tablets were tested in a USP apparatus 2 dissolution tester at 37° C. in 500 ml 0.1N HCl to simulate gastric conditions. The tablet expand in about 15 minutes to dimensions of 22×10×23 mm, large enough to effect gastric retention. The results of the release of the alendronate are given in Table 9.

Essentially no alendronate was released during the first three hours. The drug was then released at a relatively constant pace from the inner tablet through the GRDS matrix.

TABLE 9

Time (h)	Cumulative % release
0	0
1	0
2	0
3	5
4	15
5	30
6	50
7	65
8	75
9	80
12	100

Example 12

Sodium alendronate monohydrate was granulated with 0.5% HPC (Klucel HF) in ethanol. The granulate was dried and milled to a free flowing powder. This granulate was mixed with the GRDS matrix formulation of Table 7 in a ratio of 11.8 mg alendronate granulate to 850 mg GRDS matrix such that the alendronate matrix was dispersed homogeneously in the matrix. Tablets were pressed in a standard rotary press using oval tooling to give tablets with an approximate size of 17×7×8 mm. 500 grams of these tablets were coated in a perforated pan coater with 5% HPMC suspended in ethanol under the following conditions to give tablets with a coating level of 15% w/w.

Coating conditions:	
Bed temperature:	40° C.
Solution flow rate:	7.5 ml/min
Coating time:	about 20 minutes

The tablets were tested in a USP apparatus 2 dissolution tester at 37° C. in 500 ml 0.1N HCl to simulate gastric conditions. The tablet expands quickly, but slower than in the previous examples (in about 45 minutes) to dimensions of 20×8×20 mm which is large enough to effect gastric retention. The results of the release of the alendronate are given in Table 10. A low level of alendronate was released during the first three hours. The drug was then released at a relatively constant pace from the GRDS matrix.

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TABLE 10

Time (h)	Cumulative % release
0	0
1	1
2	3
3	5
4	25
5	45
6	65
7	85
8	100

Example 13

Tablets from example 11 were administered to 3 beagle dogs in a crossover design versus an immediate release alendronate formulation. Urine samples were collected for 48 hours and an overall AUC for alendronate was determined. The average bioavailability of the alendronate from the immediate release formulation was calculated to be ~1.5% while the bioavailability of the gastric retention alendronate was found to be greater than 3%

We claim:

1. A pharmaceutical dosage form for oral administration to a patient which provides delayed gastric release of a therapeutically effective amount of a therapeutic bis-phosphonate, the dosage form comprising the bis-phosphonate and a drug delivery vehicle comprising a non-hydrated hydrogel, a superdisintegrant and tannic acid wherein upon contact with gastric fluid or simulated gastric fluid the non-hydrated hydrogel hydrates and the delivery vehicle expands.

2. The pharmaceutical dosage form of claim 1 wherein the superdisintegrant swells to at least double its non-hydrated volume on contact with water.

3. The pharmaceutical dosage form of claim 1 wherein the tannic acid comprises from about 2 weight percent to about 15 weight percent of the drug delivery vehicle.

4. The pharmaceutical dosage form of claim 1 wherein the bis-phosphonate either is not released or is released at a low level for a period of two hours resulting in a cumulative release of about 5% or less.

5. The pharmaceutical dosage form of claim 1 wherein the bis-phosphonate either is not released or is released at a low level for a period of three hours resulting in a cumulative release of about 5% or less.

6. The pharmaceutical dosage form of claim 1 wherein essentially no bis-phosphonate is released for a period of two hours resulting in a cumulative release after three hours of about 5% or less.

7. The pharmaceutical dosage form of claim 1 wherein the bis-phosphonate is selected from the group consisting of alendronic acid and its pharmaceutically acceptable salts and hydrates thereof, residronate, etidronate and teludronate.

8. The pharmaceutical dosage form of claim 1 wherein the bis-phosphonate is alendronic acid or one of its pharmaceutically acceptable salts and hydrates thereof.

9. The pharmaceutical dosage form of claim 8 wherein the bis-phosphonate is monosodium alendronate monohydrate.

10. The pharmaceutical dosage form of claim 8 wherein the bis-phosphonate is monosodium alendronate trihydrate.

11. The pharmaceutical dosage form of claim 8 wherein the bis-phosphonate is alendronic acid.

12. The pharmaceutical dosage form of claim 1 wherein the hydrogel comprises hydroxypropyl methylcellulose.

13. The pharmaceutical dosage form of claim 12 wherein the hydrogel further comprises hydroxypropyl cellulose.

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14. The pharmaceutical dosage form of claim 13 wherein the hydrogel comprises hydroxypropyl methylcellulose and hydroxypropyl cellulose in a weight ratio of from about 1:3 to about 5:3.

15. The pharmaceutical dosage form of claim 2 wherein the superdisintegrant is selected from the group consisting of cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl cellulose sodium and sodium starch glycolate.

16. The pharmaceutical dosage form of claim 15 wherein the superdisintegrant is sodium starch glycolate.

17. The pharmaceutical dosage form of claim 15 wherein the superdisintegrant is cross-linked carboxymethyl cellulose sodium.

18. The pharmaceutical dosage form of claim 3 wherein tannic acid comprises from about 5 weight percent to about 15 weight percent of the drug delivery vehicle.

19. A method of treating bone disease in a human patient in need of such treatment by administering to the patient the pharmaceutical dosage form of claim 1.

20. The method of claim 19 wherein the bone disease is metastatic bone disease.

21. The method of claim 19 wherein the bone disease is osteoporosis.

22. The method of claim 19 wherein the bone disease is Paget's disease.

23. A method of inhibiting bone resorption in a human patient in need of such treatment by administering to the patient the pharmaceutical dosage form of claim 1.

24. A method of treating hypercalcemia in a human patient in need of such treatment by administering to the patient the pharmaceutical dosage form of claim 1.

25. A method of treating malignancy in bone of a human patient in need of such treatment by administering to the patient the pharmaceutical dosage form of claim 1.

26. The pharmaceutical dosage form of claim 1 wherein the drug delivery vehicle comprises of from about 50 wt. % to about 80 wt. % of a hydrogel, of from about 10 wt. % to about 30 wt. % of a superdisintegrant, and of from about 5 wt. % to about 10 wt. % tannic acid.

27. The pharmaceutical dosage form of claim 26 capable of being retained in the stomach of a human patient for a period of at least two hours.

28. The pharmaceutical dosage form of claim 26 capable of being retained in the stomach of a human patient for a period of at least three hours.

29. The pharmaceutical dosage form of claim 26 wherein the dosage form swells by a factor of five or more within about fifteen minutes of contacting aqueous solution.

30. The pharmaceutical dosage form of claim 29 wherein the dosage form swells by a factor of eight or more within about fifteen minutes of contacting aqueous solution.

31. The pharmaceutical dosage form of claim 29 wherein the dosage form swells by a factor of five or more within about five minutes of contacting aqueous solution.

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32. The pharmaceutical dosage form of claim 26 further comprising a substance that emits gas upon contact with acid.

33. The pharmaceutical dosage form of claim 32 wherein the substance that emits gas upon contact with acid is sodium bicarbonate.

34. The pharmaceutical dosage form of claim 26 wherein the hydrogel comprises hydroxypropyl methylcellulose.

35. The pharmaceutical dosage form of claim 34 wherein the hydrogel further comprises hydroxypropyl cellulose.

36. The pharmaceutical dosage form of claim 35 wherein the hydrogel comprises hydroxypropyl methylcellulose and hydroxypropyl cellulose in a weight ratio of from about 1:3 to about 5:3.

37. The pharmaceutical dosage form of claim 26 wherein the superdisintegrant is selected from the group consisting of cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl cellulose sodium and sodium starch glycolate.

38. A coated pharmaceutical dosage form comprising a core which contains a therapeutic bis-phosphonate and optionally other pharmaceutical excipients and a coating around the core, wherein the coating comprises a hydrogel, a superdisintegrant and tannic acid.

39. The coated pharmaceutical dosage form of claim 38 comprising from about 50 wt. % to about 80 wt. % of a hydrogel, from about 10 wt. % to about 30 wt. % of a superdisintegrant, and from about 5 wt. % to about 10 wt. % tannic acid.

40. A coated pharmaceutical dosage form having a core comprising about 18 wt. % sodium alendronate monohydrate, about 48 wt. % microcrystalline cellulose and about 32 wt. % lactose, the core having a coating thereon which comprises about 17 wt. % HPMC, about 10 wt. % tannic acid, about 50 wt. % HPC and about 22 wt. % crosslinked carboxymethyl cellulose sodium.

41. A coated pharmaceutical dosage form having a core comprising about 18 wt. % sodium alendronate monohydrate, about 41 wt. % microcrystalline cellulose and about 41 wt. % lactose, the core having a coating thereon which comprises about 17 wt. % HPMC, about 10 wt. % tannic acid, about 50 wt. % HPC and about 22 wt. % crosslinked carboxymethyl cellulose sodium.

42. A method of making the dosage form of claim 40 or 41 comprising the steps of mixing powdered sodium alendronate monohydrate, microcrystalline cellulose and lactose, tableting the mixed powders to make a core, dry mixing the HPMC, tannic acid, HPC and cross-linked carboxymethyl sodium to produce a coating mix, embedding the core in the coating mix and compacting the coating mix to produce the dosage form.

* * * * *

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,

Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC.

Defendant.

C.A. No. 01-048-JJF
(Consolidated)

**MERCK & CO., INC.'S FIRST SET OF REQUESTS
FOR PRODUCTION OF DOCUMENTS AND THINGS (NOS. 1-60)
TO DEFENDANT TEVA PHARMACEUTICALS USA, INC.**

Pursuant to Rule 34 of the Federal Rules of Civil Procedure, Plaintiff Merck & Co., Inc. ("Merck") requests that Defendant Teva Pharmaceuticals USA, Inc. produce for inspection and copying the following documents and things in their possession, custody, or control. The requested documents and things are to be made available for inspection, copying, and/or photographing at the offices of HOWREY SIMON ARNOLD & WHITE, LLP, 750 Bering Drive, Houston, Texas 77057, thirty (30) days after the service hereof, or at such other time and location as may be mutually agreed upon by the parties. Documents either shall be produced as required by Rule 34.

DEFINITIONS AND INSTRUCTIONS

The following definitions and instructions are applicable to terms employed in this set of requests:

A. These requests require you to produce all documents and things that are in your actual or constructive possession, custody, or control or in the possession, custody or control of your attorneys, accountants, representatives, consultants, agents, employees, or anyone else acting on your behalf.

B. The term "DOCUMENT" shall have the broadest meaning possible under the Federal Rules of Civil Procedure and shall include, but not be limited to, the original (or a copy when the original is not available), each non-identical copy (including those which are non-identical by reason of notations or markings, or by appearing in the files of a separate person), and any books, notebooks, pamphlets, periodicals, letters, reports, memoranda, handwritten notes, notations, messages, telegrams, wires, cables, press or news wire releases, records, studies, analyses, summaries, magazines, booklets, circulars, labels, catalogs, bulletins, instructions, operating or maintenance manuals, operating or product specifications, fabrication sheets, calendars, day-timers, notes or records of meetings, notices, purchase orders, bills, ledgers, checks, tabulations, questionnaires, surveys, drawings, sketches, schematics, blueprints, flow sheets, working papers, charts, graphs, indices, tapes, agreements, releases, appraisals, valuations, estimates, opinions, financial statements, accounting records, income statements, photographs, films or videotapes, tapes, minutes, contracts, leases, invoices, records of purchase or sale, correspondence, electronic or other transcription or taping of or notes pertaining to telephone or personal conversations or conferences, tape recordings, electromagnetic recordings, voice mail messages or transcriptions thereof, interoffice and intraoffice communications of all types, E-mail messages or printouts thereof, microfilms, CD ROMs, videotapes or cassettes, films, movies, computer printouts and all other written, printed, typed, punched, engraved, taped, filmed, recorded (electronically or otherwise), labeled, or graphic matter or thing, of whatever description, however produced or reproduced (including computer-stored or generated data, together with instructions or programs necessary to search and retrieve such data), and shall include all attachments to (including tangible things) and enclosures with (including tangible

things) any requested item, to which they are attached or with which they are enclosed, and each draft thereof.

C. The term "THING" refers to any tangible object, other than a DOCUMENT, and includes objects of every kind and nature including, but not limited to, prototypes, models, samples and specimens.

D. These requests shall include DOCUMENTS and THINGS created, acquired, or identified up to the date(s) of production and shall be deemed to be continuing. Therefore, Defendant shall promptly produce to Merck, as supplemental responses to these requests in accordance with FED. R. CIV. P. 26(e), any additional DOCUMENTS or THINGS that Defendant identify, acquire, or become aware of up to and including the time of trial.

E. The term "communications" includes all discussions, conversations, interviews, negotiations, facsimiles, cablegrams, mailgrams, telegrams, telexes, cables or other forms of written or verbal interchange, however transmitted, including reports, notes, memoranda, lists, agenda, and other documents and records of communications, and when used shall require a statement of the name of the individual who made the communication, the person(s) to whom he made it, the date it was made, the form in which it was made, and whether or not it was recorded.

F. Where identification of a DOCUMENT or THING is requested, such identification should be sufficient for the characterization of the DOCUMENT or THING in a request by Merck for production of DOCUMENTS under Rule 34 of the Federal Rules of Civil Procedure and should include, without limitation, the following information:

1. identification of the author or maker;
2. the date that the DOCUMENT or THING was generated;

3. the general nature of the DOCUMENT or THING, i.e., whether it is a letter, a memorandum, a photograph, etc.;
4. identification of the PERSON to whom the original was addressed;
5. identification of all recipients;
6. the identity of the PERSON now having possession of the original DOCUMENT or THING and the location of the original; and
7. the identity of each PERSON now having possession of a copy of the DOCUMENT or THING and the location of each such copy.

G. The word "PERSON" or "PERSONS" shall mean an individual, corporation, proprietorship, partnership, association, joint venture, or any other entity.

H. Where identification of a PERSON is required, such identification shall, without limitation, include the following information:

1. the PERSON's full name;
2. whether it is an individual, corporation, proprietorship, partnership, association, or other entity;
3. current or last known business address;
4. if the PERSON is an individual, the individual's home address, or if it is not known, the individual's last known home address; and
5. if the PERSON is an individual, the individual's present employer and position.

1. "Teva USA" shall mean Teva Pharmaceutical USA, Inc., and shall include (a) any divisions, departments, parents, subsidiaries, other organizational or operational units, and agents of Teva Pharmaceutical USA, Inc.; (b) all predecessor or successor companies or corporations; (c) all companies, corporations, partnerships, associations, or other business entities which are or have been under the common ownership or control, in any manner, Teva Pharmaceutical USA, Inc. and (d) each of the present and former officers, directors, employees, agents, attorneys, or other representatives of any of them.

J. “Defendant” shall mean Teva USA.

K. In the event Defendant claims that a request is overly broad, Defendant is requested to respond to that portion of the request which is unobjectionable and specifically identify the respect in which the request is allegedly overly broad.

L. In the event Defendant claims that a request is unduly burdensome, Defendant is requested to respond to that portion of the request which is unobjectionable and specifically identify the respect in which the request is allegedly unduly burdensome.

M. With respect to any DOCUMENT or THING that Defendant is unwilling to produce for inspection by Merck’s counsel because the DOCUMENT or THING is asserted to be immune from discovery under the attorney-client privilege or work-product immunity, state separately with respect to each such DOCUMENT or THING sufficient information to disclose:

1. the general nature of each such DOCUMENT and/or THING, i.e., whether it is a letter, memorandum, report, pamphlet, etc.;
2. the date on which each such DOCUMENT and/or THING was reproduced or transcribed;
3. the name and business address of the PERSON who signed or prepared each such DOCUMENT and/or THING or both and the name and business address of each such PERSON who has edited, corrected, revised, or amended the same;
4. the name and business address of each PERSON to whom any such DOCUMENT or THING was given or sent, or otherwise known to Defendant as being an intended or actual recipient of a copy thereof;
5. the name and address of the PERSON having possession, custody, or control of each such DOCUMENT or tangible THING;
6. a brief indication of the subject matter of each such DOCUMENT or THING; and
7. the grounds for the claimed privilege or immunity as to each such DOCUMENT or THING.

N. For any requested DOCUMENT that has been destroyed after January 25, 2001, Defendant shall identify each DOCUMENT, set forth the contents of each destroyed DOCUMENT, the date of such destruction, the identity of any individuals who authorized the destruction, and other circumstances related to such destruction.

O. “The term ‘077 patent” refers to U.S. Patent No. 4,621,077, entitled “Pharmacologically Active Biphosphonates, Process for the Preparation Thereof and Pharmaceutical Compositions Therefrom.”

P. “The term ‘941 patent” refers to U.S. Patent No. 5,358,941, entitled “Dry Mix Formulation for Bisphosphonic Acids with Lactose.”

Q. “The term ‘590 patent” refers to U.S. Patent No. 5,681,590, entitled “Dry Mix Formulations for Bisphosphonic Acids.”

R. “The term ‘726 patent” refers to U.S. Patent No. 5,849,726, entitled “Anhydrous Alendronate Monosodium Salt Formulations.”

S. “The term ‘207 patent” refers to U.S. Patent No. 6,008,207, entitled “Anhydrous Alendronate Monosodium Salt Formulations.”

T. “The ‘410 patent” refers to U.S. Patent No. 6,090,410, entitled “Dry Mix Formulations for Bisphosphonic Acids.”

U. “The ‘329 patent” refers to U.S. Patent No. 5,994,329, entitled “Method for Inhibiting Bone Resorption.”

V. “The ‘801 patent” refers to U.S. Patent No. 6,015,801, entitled “Method for Inhibiting Bone Resorption.”

W. “The ‘294 patent” refers to U.S. Patent No. 6,225,294 B1, entitled “Method for Inhibiting Bone Resorption.”

X. The term “patents-in-suit” refers to the ‘077, ‘941, ‘590, ‘726, ‘410, ‘801, ‘329, ‘294, and ‘207 patents.

Y. The term “Abbreviated New Drug Applications” refers to an Abbreviated New Drug Application filed with the Food and Drug Administration.

Z. “FDA ” refers to the United States Food and Drug Administration.

AA. “Prior art” solely for the purpose of Merck’s requests shall mean any publication or activity predating the applicable date of filing for each of the patents-in-suit dealing with alendronate or any other pharmaceutically active biphosphonates and including but not limited to any publication or activity falling within 35 U.S.C. § 102 with respect to any of the patents-in-suit.

BB. The term “alendronate” means 4-amino-1-hydroxybutane-1,1-biphosphonic acid, any analog, and includes its monosodium acid salt form.

CC. A document or communication “relating to,” “related to,” or “concerning” a given subject means all documents or communications that constitute, contain, embody, comprise, reflect, identify, state, refer to, deal with, comment on, mention, respond to, describe, involve, or are in any way pertinent to that subject, including, but not limited to, documents concerning the presentation of other documents.

DD. “Any” or “each” should be understood to include and encompass “all”; “or” should be understood to include and encompass “and”; and “and” should be understood to include and encompass “or”.

EE. The use of the singular form of any word includes the plural and vice versa.

FF. For purposes of these requests, terms not specifically defined shall be given their ordinary meaning. Should Defendant be unable to understand the meaning of any term Defendant is invited to immediately seek its clarification through Merck's counsel.

REQUESTS FOR PRODUCTION

DOCUMENT REQUEST NO. 1

All opinions, legal or otherwise, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other affirmative defense.

DOCUMENT REQUEST NO. 2

All documents and things, including correspondence with counsel, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other affirmative defense.

DOCUMENT REQUEST NO. 3

All documents and things relating to patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of any of the patents-in-suit.

DOCUMENT REQUEST NO. 4

All opinions, legal or otherwise, relating to the validity of the patent term extension or the patent term restoration of the '077 patent.

DOCUMENT REQUEST NO. 5

All documents and things, including correspondence with counsel, relating to validity of the patent term extension or the patent term restoration of the '077 patent to Defendant.

DOCUMENT REQUEST NO. 6

All documents and things relating to any policies or practices of Defendant concerning patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of the patents of others.

DOCUMENT REQUEST NO. 7

All Abbreviated New Drug Applications filed by Defendant with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 8

All supplements and amendments to Abbreviated New Drug Applications filed by Defendant with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 9

All documents and things relating to or constituting correspondence or other communications, including but not limited to draft documents and correspondence, among Defendant and/or between Defendant and/or any other person and any foreign or domestic regulatory agency including, but not limited to, the FDA or a foreign counterpart concerning alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 10

All documents and things relating to the patent certifications made by Defendant as part of an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 11

All documents and things relating to Defendant's decision to file an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active

biphosphonate formulations, including, but not limited to, the timing of the filing, the cost for the filing, and any cost or benefit analysis.

DOCUMENT REQUEST NO. 12

All documents and things relating to the timing, schedule, timetable or projection of approval of Defendant's Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 13

All documents and things relating to any labeling, promotion, advertising or claims by Defendant for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S or any other country.

DOCUMENT REQUEST NO. 14

All documents and things relating to Defendant's decision for file a patent certification as part of an Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulation.

DOCUMENT REQUEST NO. 15

All documents and things relating to FDA notification of "tentative approval" of the Abbreviated New Drug Application for Defendant's alendronate formulations.

DOCUMENT REQUEST NO. 16

All documents and things relating to the patents-in-suit.

DOCUMENT REQUEST NO. 17

All documents and things relating to the first awareness of the patents-in-suit by Defendant.

DOCUMENT REQUEST NO. 18

All documents and things created before the filing of this suit concerning or constituting any prior art search relating to any of the patents-in-suit.

DOCUMENT REQUEST NO. 19

All prior art that Defendant contend supports an allegation that any claim of the patents-in-suit is invalid.

DOCUMENT REQUEST NO. 20

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are not, and/or will not be, infringed by Defendant.

DOCUMENT REQUEST NO. 21

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are unenforceable.

DOCUMENT REQUEST NO. 22

All documents and things forming the basis of, or relating to, any and all defenses pleaded by Defendant that any claim of the patents-in-suit is invalid.

DOCUMENT REQUEST NO. 23

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as lacking a written description.

DOCUMENT REQUEST NO. 24

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as the specification does not enable the claims.

DOCUMENT REQUEST NO. 25

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as indefinite.

DOCUMENT REQUEST NO. 26

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as lacking utility.

DOCUMENT REQUEST NO. 27

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are anticipated by the prior art.

DOCUMENT REQUEST NO. 28

All documents and things forming the basis of, or relating to, Defendant's certification that any of the patents-in-suit are invalid as obvious in light of the prior art.

DOCUMENT REQUEST NO. 29

All documents and things relating to the April 21, 1997 patent term restoration of the '077 patent under 35 U.S.C. § 156.

DOCUMENT REQUEST NO. 30

All documents related to Defendant's patent certification and Notice of Patent Certification for Abbreviated New Drug Applications for alendronate formulations.

DOCUMENT REQUEST NO. 31

All documents and things relating to any legal or administrative proceedings concerning the manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active biphosphonate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 32

All documents and things concerning any indemnification and/or insurance provided to, received, or granted by Defendant against or for the infringement of any of the patents-in-suit.

DOCUMENT REQUEST NO. 33

All documents and things relating to Defendant's production or attempted production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 34

All documents relating to research and development of manufacturing processes for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 35

All documents and things relating to or comprising communications among Defendant and/or between Defendant and any other person concerning the design, development, testing, structure, function and/or operation of manufacturing facilities for the production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 36

All documents and things relating to U.S. or foreign lawsuits, pending or previously resolved, or investigations regarding Defendant's production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 37

All documents and things relating to any manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active biphosphonate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 38

All documents and things relating to any supply agreement for alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 39

All documents and things constituting or relating to negotiations between Defendant and suppliers or potential suppliers of alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 40

All documents and things relating to any desire, consideration or need by Defendant to obtain or not obtain a license under any of the patents-in-suit.

DOCUMENT REQUEST NO. 41

All documents and things constituting or relating to licenses and/or agreements for alendronate or any other pharmaceutically active biphosphonate among Defendant and/or between Defendant and any other person.

DOCUMENT REQUEST NO. 42

All documents and things related to licensing agreements among Defendant and/or between Defendant and any other person for the production, distribution or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 43

All documents and things concerning marketing or whether to market alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 44

All documents and things relating to market share and market potential for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 45

All documents and things relating to the dollar amounts expended by Defendant or any other person for the promotion of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 46

All documents and things relating to all forms of promotions for or marketing of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country by Defendant or any other person.

DOCUMENT REQUEST NO. 47

All documents and things created after January 1, 1993, relating to any market survey, market analysis, sales projections or forecast of customer demand with respect to alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

DOCUMENT REQUEST NO. 48

All documents and things relating to any communications to or from Defendant's sales forces, agents, dealers, representatives, distributors, the press, or any news wire service relating to this lawsuit, and/or any of the patents-in-suit.

DOCUMENT REQUEST NO. 49

All documents and things relating to research and development of alendronate and alendronate formulations or any other pharmaceutically active biphosphonate and its formulations.

DOCUMENT REQUEST NO. 50

Two hundred alendronate tablets for each dosage form produced by Defendant for the purpose of obtaining FDA approval.

DOCUMENT REQUEST NO. 51

All documents and things relating to any tests comparing Merck's alendronate product with the alendronate product that Defendant produced.

DOCUMENT REQUEST NO. 52

Any samples of Merck products that contain alendronate or any other pharmaceutically active biphosphonate that have been tested or examined by Defendant or any persons working on their behalf.

DOCUMENT REQUEST NO. 53

All documents and things relating to any testing performed using Merck's alendronate product.

DOCUMENT REQUEST NO. 54

All documents and things relating to Defendant's knowledge of Merck's activities in the research, patenting, development, manufacture, use or sale of any pharmaceutical formulation of alendronate or any other pharmaceutically active biphosphonate.

DOCUMENT REQUEST NO. 55

All documents and things Defendant contemplate introducing at trial.

DOCUMENT REQUEST NO. 56

All documents and/or things relating to any experts Defendant contemplate calling at trial, including but not limited to the educational and technical training of each expert and any publications authored by such expert.

DOCUMENT REQUEST NO. 57

All documents and things, including but not limited to organizational charts, showing identity and job titles of employees since January 1, 1993 to the present for all of Defendant's divisions and/or subsidiaries involved in the research, development, production, design, manufacture or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

DOCUMENT REQUEST NO. 58

All documents and things setting forth Defendant's document retention and/or destruction policies.

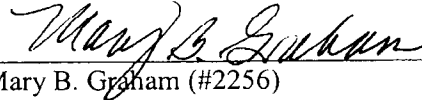
DOCUMENT REQUEST NO. 59

All documents and things relating to or constituting applications by Defendant to obtain regulatory approval for alendronate or any other pharmaceutically active biphosphonate in a foreign country.

DOCUMENT REQUEST NO. 60

Two grams of each ingredient in the alendronate tablets produced by Defendant
for the purpose of obtaining FDA approval.

MORRIS, NICHOLS, ARSHT & TUNNELL



Mary B. Graham (#2256)
Maryellen Norcika (#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200

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March 19, 2002

279874

CERTIFICATE OF SERVICE

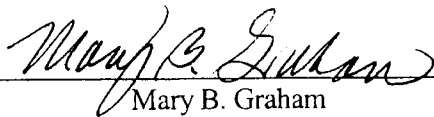
The undersigned hereby certifies that true and correct copies of the foregoing were caused to be served on March 19, 2002 upon the following individuals:

BY HAND:

Josy W. Ingersoll, Esquire
Young Conaway Stargatt & Taylor, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

BY FACSIMILE:

James Galbraith, Esquire
Kenyon & Kenyon
One Broadway
New York, NY 10004



Mary B. Graham

EXHIBIT C



Danae M. Schuster
(212) 908-6090
dschuster@kenyon.com

One Broadway
New York, NY 10004-1050
212.425.7200
Fax 212.425.5288

October 9, 2002

VIA FACSIMILE: (713) 787-1440
Confirmation by Post

Scott Garber, Esq.
HOWREY SIMON ARNOLD & WHITE, L.L.P.
750 Bering Drive
Houston, TX 77057-2198

Re: Merck v. Teva

Dear Scott:

I have your letters of September 13, 2002 and September 25, 2002. With respect to your concern about Teva's document production, we confirmed that all additional responsive documents have now been produced. Enclosed please find Teva's documents bearing production numbers T 007117 to T 007146, Teva's most recent draft of its package insert.

Contrary to your assertions in your letter of September 25, 2002, Ms. Jaskot was prepared and did adequately answer questions relating to Topics 6 and 7 of Merck's Rule 30(b)(6) notice of August 21, 2002 (*see, e.g.*, pp 94-96, 109:14-110:5, 120-124, 131-134). In addition, as Ms. Jaskot testified, she was fully aware that she had been designated as Teva's corporate representative for Topic 7 (*see* p11:5-6).

Sincerely,

A handwritten signature in black ink, appearing to be 'Danae M. Schuster', written over a horizontal line.

Danae M. Schuster

cc: Jason Abair, Esq. (w/o enclosures)



One Broadway
New York, NY 10004-1050
212.425.7200
Fax 212.425.5288

Fax Transmission

From: **Danae M. Schuster**

Date: **October 9, 2002**

Direct Dial: **212.908.6090**

Fax: **212.425.5288**

Total number of pages: **31**
(including cover)

Please deliver to:

Name	Company	Fax	Phone
Scott Garber	Howrey Simon Arnold & White, L.L.P.	(713) 787-1440	(713) 787-1400
Jason Abair, Esq.	Howrey Simon Arnold & White, L.L.P.	(713) 787-1440	(713) 787-1400

Comments:

☐ Original will not follow ☐ Original will follow by ☐ Regular Mail ☐ Overnight Delivery ☐ Hand Delivery

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New York Washington, DC Silicon Valley www.kenyon.com

EXHIBIT D



Maria Luisa Palmese
(212) 908-6444
mpalmese@kenyon.com

One Broadway
New York, NY 10004-1050
212.425.7200
Fax 212.425.5288

December 11, 2002

VIA FACSIMILE: (713) 787-1440

Confirmation by DHL Courier

Nicolas G. Barzoukas, Esq.

HOWREY SIMON ARNOLD & WHITE, L.L.P.

750 Bering Drive

Houston, TX 77057-2198

Re: *Merck v. Teva*

Dear Nick:

I have Jason Abair's letter dated December 10, 2002.

As discussed yesterday, I confirm that Teva has conducted a diligent search for documents responsive to Merck's document requests for all persons at Teva involved with the development of Teva's weekly alendronate sodium after the complaint in this action was filed and again after Merck served its document requests on Teva.

I also confirm that Teva agrees to exchange its source log with Merck on Friday, December 13, 2002.

As we have now complied with your requests, we expect that Merck will withdraw its motion to compel today.

Sincerely,

A handwritten signature in black ink, appearing to read 'MLP', followed by a long horizontal line.

Maria Luisa Palmese

cc: Jason C. Abair, Esq. (via facsimile)

CERTIFICATE OF SERVICE

The undersigned hereby certifies that true and correct copies of the foregoing were caused to be served on April 11, 2003, upon the following counsel of record:

VIA HAND DELIVERY

Josy Ingersoll, Esq.
Adam Poff, Esq.
YOUNG CONAWAY STARGATT & TAYLOR, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801 Fax: (302) 571-1253

VIA FEDERAL EXPRESS

James Galbraith, Esq.
KENYON & KENYON
One Broadway
New York, NY 10004
Fax: (212) 425-5288



Mary B. Graham

EXHIBIT L

CLERK U.S. DISTRICT COURT
DISTRICT OF DELAWAREIN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,)

Plaintiff,)

v.)

Civil Action No. 01-048-JJF)

TEVA PHARMACEUTICALS USA, INC,)

Defendant.)

**MERCK'S MOTION TO ADD TEVA'S PATENT APPLICATION NO.
WO 03/057136 TO THE RECORD AS PLAINTIFF'S TRIAL EXHIBIT 302**

On July 22, 2003, this Court granted Merck's post-trial motion to add to the trial record as PTX 301 Teva's U.S. Patent No. 6,476,006, which Teva had failed to produce during discovery and which Merck learned of only after trial. That patent contradicts positions that Teva espoused at trial on the key issue of whether, before Merck's invention, unit doses of alendronate sodium sevenfold larger than the daily doses were expected to exacerbate the upper gastrointestinal side effects associated with the drug. Merck has now discovered another equally relevant Teva patent application that Teva failed to produce during discovery in this case. This just-published patent application, too, contradicts Teva's position at trial that Merck's once-weekly invention would have been obvious because allegedly no such exacerbation of side effects was expected and corroborates the testimony of Merck's experts about the expectation of side effects. Merck hereby moves to have Teva's PCT patent application WO 03/057136 (the "'136 application") (Exhibit A) added to the trial record as Plaintiff's Trial Exhibit 302.

FILED
CLERK U.S. DISTRICT COURT
DISTRICT OF DELAWARE
2003 AUG 22 PM 3:50

TEVA'S '136 APPLICATION

The '136 application was filed on behalf of Teva on November 12, 2002. Teva's designated agents in charge of that application are Kenyon & Kenyon in New York, its litigation counsel in this case. (Exh. A, cover page) Teva's '136 application relates to a tablet dosage form for oral delivery of "ulcerative" drugs such as bisphosphonates, including alendronate, that can cause gastrointestinal injury (Exh. A, p. 1) Teva, and its trial counsel, were plainly aware and in possession of the '136 application and its underlying U.S. filing long before trial this year. Indeed, the original filing upon which the '136 application relies for priority was submitted to the U.S. Patent and Trademark Office in December 2001. Although the '136 application, its U.S. counterpart application, and all related documentation in Teva's possession were responsive to Merck's discovery requests, Teva failed to provide them in this case.¹ Instead, Merck has only just discovered on its own the '136 application, which published on July 17, 2003.

The '136 application is highly relevant. At trial, Merck countered Teva's obviousness arguments with evidence that, before Merck's invention, unit doses of alendronate sodium sevenfold the daily dose would not have been considered safe and tolerable for the management of osteoporosis, including evidence of the long and widely accepted history of the gastrointestinal side effects of bisphosphonates as a class of compounds. Teva vehemently disputed Merck's position, repeatedly belittling it as a "fear defense." Teva even characterized Merck's evidence as "scientifically unsound." (Teva's Post-Trial Reply Brief at p. 21) The '136 application, however, directly contradicts Teva's position and confirms the correctness of the

¹ The '136 application and counterpart was responsive to several Merck document requests, including Nos. 13, 16, 31, 34 and 49. A copy of Merck's First Set of Document Requests was attached as Exhibit B to Merck's Motion to Add Teva's U.S. Patent No. 6,476,006 to the Record as Plaintiff's Trial Exhibit 301, filed April 11, 2003 (D.I. 144).

opinions of Merck's experts, Drs. Papapoulos and Fennerty, with respect to the gastrointestinal side effects of bisphosphonates in general, and alendronate in particular.

More particularly, to support the claimed invention of the '136 application to "improved solid dosage forms for oral delivery of drugs that cause contact irritation or ulceration to the lining of the esophagus and stomach," Teva's application begins by noting that "[g]astrointestinal side effects are a common and serious problem with many drugs" (Exh. A, p. 1). Teva then states that "[m]any drugs have been shown to cause damage" to the esophagus or stomach (*id.*). Highlighted as a class of drugs "known to cause such damage" are bisphosphonates, including alendronate, which is the only bisphosphonate Teva cites specifically (Exh. A, pp. 1-2). Teva further describes bisphosphonates in general, and alendronate in particular, as "*ulcerative.*" (Exh. A, pp. 5,7) Indeed, Teva states (Exh. A, p. 7):

Preferred embodiments of the invention are well suited for the administration of ulcerative drugs. As used in this disclosure, the term "ulcerative" in reference to an active pharmaceutical ingredient, drug or excipient means that, when the drug or excipient is contacted as a solid with the mucosa lining, at least a portion of the gastrointestinal tract is causes [sic] erosive damage. *Alendronate, other bisphosphonates and NSAIDS that non-selectively inhibit the COX-1 and COX-2 enzyme are ulcerative drugs.*

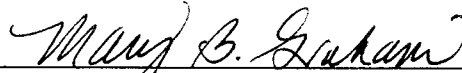
This detailed background laid out in the application, with citations to numerous scientific references, shatters Teva's argument to the Court that the gastrointestinal side effect profiles of other bisphosphonates are not relevant to alendronate. It is clear from the '136 application (and PTX 301) that Teva, other than at trial, agrees with Merck that alendronate shares its side effect profile with other bisphosphonates:

TEVA'S TRIAL POSITION	TEVA'S POSITION IN THE WITHHELD '136 APPLICATION
<p>“[D]ata from the older [bisphosphonate] compounds are irrelevant [to alendronate] and reference to them unnecessary.” [Teva's Post-Trial Reply Brief, at p. 18].</p> <p>and</p> <p>“Merck's arguments based on discredited attempts to extrapolate from non-analogous observations about remotely related [bisphosphonate] compounds are scientifically unsound and should be rejected.” [Teva's Post-Trial Reply Brief, at p. 21].</p>	<p>“There are some indications in the literature that among the bisphosphonates, alendronate does not cause ulceration. [citations omitted] However, <i>the great weight of the literature indicates that alendronate shares this feature with the other bisphosphonates.</i>” [citations omitted] [Exh. A at p. 2 (emphasis added)]</p>

The legal analysis as to why Teva's withheld '136 application should be added to the trial record is identical to that set out in Merck's Motion to Add Teva's U.S. Patent No. 6, 476,006 to the Record as Plaintiff's Trial Exhibit 301. Accordingly, Merck asks that the '136 application be admitted into the trial record.²

² When we asked Teva if it would agree to the addition of the '136 application to the trial record, Teva said it would “not oppose a motion to do so,” unless Merck intended to include any “substantive characterization of the document,” in which case Teva said it would oppose the motion (Exh. B). But to submit the exhibit without reference to the relevant passages and an explanation of the document's relevance would require the Court to fend for itself and would impose on the Court the burden of reviewing the entire 41-page patent application without a road map. Of course, had Teva produced the document when it should have, Merck and the Court would both long ago have had the benefit of testimony and briefing on the document.

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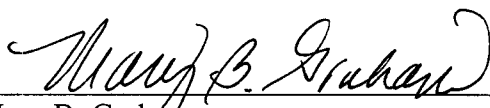
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CERTIFICATE PURSUANT TO LOCAL RULE 7.1.1

The undersigned hereby certifies that counsel for Merck & Co., Inc. attempted to reach agreement with Teva's counsel on the foregoing motion and counsel were unable to reach agreement.



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EXHIBIT A

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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: DOSAGE FORM WITH A CORE TABLET OF ACTIVE INGREDIENT SHEATHED IN A COMPRESSED ANNULAR BODY OF POWDER OR GRANULAR MATERIAL, AND PROCESS AND TOOLING FOR PRODUCING IT

(57) Abstract: A solid dosage form for oral administration to a patient comprising a core tablet sheathed in an annular body of compressed powder or granular material is provided. A preferred embodiment of the solid dosage form reduces contact of the active ingredient in solid form with the mucosa lining the gastrointestinal tract, which is particularly advantageous for delivering an ulcerative drug. A tool set comprising a columnar punch and a punch assembly comprising an annular punch and core rod, and a tableting process for making the solid dosage form are also provided.

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**DOSAGE FORM WITH A CORE TABLET OF ACTIVE INGREDIENT
SHEATHED IN A COMPRESSED ANNULAR BODY OF POWDER OR
GRANULAR MATERIAL, AND PROCESS AND TOOLING FOR PRODUCING
IT**

5

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional application Serial Number 60/342,442, filed December 24, 2001, and provisional application Serial Number 60/361,821, filed March 4, 2002, both of which are incorporated herein by reference.

10

FIELD OF THE INVENTION

The present invention relates to powder molding, pharmaceutical dosage forms, tableting processes and equipment, and improved solid dosage forms for oral delivery of drugs that cause contact irritation or ulceration to the lining of the esophagus and stomach.

15

BACKGROUND OF THE INVENTION

|| Gastrointestinal side effects are a common and serious problem with many drugs. ||
These side effects may manifest themselves in nausea or diarrhea or with injury to the gastrointestinal mucosa. Many drugs have been shown to cause damage to the mucosal
20 lining of the esophagus (esophagitis) or the stomach (gastritis). Among the drugs known to cause such damage are non-steroidal anti-inflammatory drugs ("NSAIDs"). See A.A. al-Quorain et. al., "Non Steroidal Anti-inflammatory Drug Induced Gastropathy", *J. Int. Med. Res.* **1993**, *21*(2), 89 – 97; P. M. Goggins et. al., "Prevalence of Helicobacter Pylori Infection and its Effect on Symptoms and non-Steroidal Anti-inflammatory Drug Induced
25 Gastro-intestinal Damage in Patients with Rheumatoid Arthritis" *Gut*, **1993**, *34*(12), 1677 – 80; M. Frezza et. al., "The Histopathology of Non- Steroidal Anti-inflammatory Drug Induced Gastroduodenal Damage: Correlation with Helicobacter Pylori, Ulcers and Haemorrhagic Events" *J. Clin. Pathol.* **2001**, *54*(7), 521-5 and references therein. Other
|| drugs known to cause such damage are bisphosphonates. See K. O. Larsen, ||
30 "Oesophagusskader Relatert till Bisphosphonater" *Tidsskr. Nor. Laegeforen* **2000**, *120*(20), 2397-9; D. Y. Graham, H. M. Malaty, "Alendronate and Naproxen Are Synergic for Development of Gastric Ulcers" *Arch. Inter. Med.* **2001**, *161*(1), 107-110; F. L. Lanza et. al., "Endoscopic Comparison of Esophageal and Gastroduodenal Effects of Risedronate

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and Alendronate in Postmenopausal Women" *Gastroenterology*, 2000 , 119(3), 631-8.

|| There are some indications in the literature that among the bisphosphonates, alendronate ||
 || does not cause ulceration. See D. C. Bauer et. Al., "Upper Gastrointestinal Tract Safety ||
 Profile of Alendronate: the Fracture Intervention Trial" *Arch. Intern. Med.* 2000, 160(4),
 5 || 517-25. However, the great weight of the literature indicates that alendronate shares this || *
 || feature with the other bisphosphonates. See J. K. Marshall et. al., "a Randomized
 Controlled Trial to Assess Alendronate-associated Injury of the Upper Gastrointestinal
 Tract" *Aliment. Pharmacol. Ther.* 2000, 14(11), 1451-7; D. Y. Graham, H. M. Malaty,
 "Alendronate Gastric Ulcers" *Aliment. Pharmacol. Ther.* 1999 , 13(4), 515-9; S. C.
 10 Abraham et. al., "Alendronate-associated Esophageal Injury:pathologic and Endoscopic
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 Gastric Injury and Delays Ulcer Healing in Rodents" *Life Sci.* 1998, 62(1) , 77-91; D. Y.
 Graham," Excess Gastric Ulcers Are Associated with Alendronate Therapy" *Am. J.*
Gastroenterol., 1998 , 93(8), 1395-6; R. E. Colina et. al., "A New Probable Increasing
 15 Cause of Esophageal Ulceration: Alendronate" *Am. J. Gastroenterol.* 1997, 92(4), 704-6.

The reason that esophagitis or gastritis are caused by ingesting a certain drug is not
 always apparent. Some drugs are sufficiently erosive that they can cause ulceration after
 they have dissolved in the stomach. However, in the case of NSAIDs, bisphosphonates
 and many other drugs, there is much evidence to implicate the solid form of the drug in
 20 causing the ulceration. See D. Jasperson, "Drug Induced Esophageal
 Disorders:pathogenesis, Incidence, Prevention and Management" *Drug Saf.* 2000, 22(3),
 237-249; S. J. Smith et al., "Pill-induced Esophagitis Caused by Oral Rifampin" *Ann.*
Pharmacother. 1999, 33(1), 27-31; J. W. Kikendall, "Pill Esophagitis" *J. Clin.*
Gastroenterol. 1999, 28(4), 298-305; A. Minchoa, D. S. Greenbaum, "Pill Esophagitis
 25 Caused by Non-steroidal Antiinflammatory Drugs" *Am. J. Gastroenterol.*, 1991, 86(8),
 1086-9. Such esophagitis is called pill induced esophagitis or pill esophagitis and when
 causing damage to the stomach lining can be called contact gastritis. These forms of
 mucosal damage can be mitigated by preventing the physical contact of the drug containing
 solid dose formulation with the surface of the mucosa.

30 Pill esophagitis and contact gastritis can be reduced by limiting physical contact
 between the pill containing the drug and the mucosal lining. Solutions suggested in the

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literature include coatings to limit esophageal contact, coatings to shorten esophageal transit time and improvements in tablet shape to shorten esophageal transit time. *See* A. C. Perkins et. al., "The Use of Scintigraphy to Demonstrate the Rapid Esophageal Transit of the Oval Film-coated Placebo Risendronate Tablet Compared to a Round Uncoated Placebo Tablet When Administered with Minimal Volumes of Water" *Int. J. Pharm.*, 2001, 222(2) 295-303; T. S-H. Chen, U.S. Patent Application Serial No. 2001/0036475; A.G. Daifotis et. al., U.S. Patent No. 5,994,329 (enteric coatings and film coatings through which the drug is released). Each of these methods has a drawback. Coatings that come off in the stomach may be removed earlier than planned while in the esophagus leading to esophagitis. Furthermore, such coatings will not prevent gastritis. Coatings or shape improvements that shorten esophageal transit time can help prevent esophagitis but again not gastritis. Enteric coatings can totally envelope the pill until it is in the small intestine. While this can prevent contact esophagitis or gastritis it will not protect against ulceration in the small intestine and will not be desired for a drug whose absorption site is in the upper part of the GI tract (stomach or duodenum).

A further suggestion to prevent contact between the solid particles of the drug formulation and the mucosal lining is to encapsulate the drug totally in a capsule or coating and release the drug slowly through an orifice or through the film coat by diffusion or through micropores. These suggestions can be fulfilled by using an osmotic pump device to deliver the drug or a permeable film coat such as Eudragit NE or Eudragit RL or RS. The osmotic pump idea is not a promising solution to the problem of contact esophagitis and gastritis. While the drug leaves the osmotic pump in solution in most cases, the osmotic agents themselves are ulcerative in high concentrations. The stream of drug plus osmotic agent leaving the orifice causes ulceration, especially if the device has lodged against the mucous membrane *See* V. Simko et. al., "Increased Risk in Esophageal Obstruction with Slow Release Medications" *J. Assoc. Acad. Minor. Phys.*, 1997, 8(2), 38-42. A permeable film coat can serve as a solution to the problem but it limits the drug release profile attainable since only relatively slower release profiles will be obtained and immediate release, or very short slow release profiles are not compatible with the film coat.

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In view of the foregoing, it would be highly desirable to have a versatile solid dosage form that reduces contact between the lining of the gastrointestinal tract and a drug contained in the dosage form, particularly an ulcerative drug. Accordingly, one object of the present invention is to provide a solid dosage form that can release a drug according to a predetermined release profile and reduce contact of the solid drug with the lining of the gastrointestinal tract during transit of the dosage form through the esophagus, stomach and intestine.

A novel set of tooling and tableting process have been invented to produce a dosage form meeting the foregoing stringent requirements on tableting presses that are presently available from commercial sources. Tableting presses are well known and available in many designs, and with an array of features. Some presses with high throughput capacity are designed for large production runs. Others are adapted for application of compression coatings, production of multilayer tablets or engraving. Design features which are desirable in presses to be used with the novel toolset of this invention will become apparent from consideration of the detailed description of the preferred embodiments of the invention which follows.

U.S. Patent No. 5,071,607 describes a pair of dies (punches) with piercing means biased into a sheathed position, which, when used to compress a coating about an object, pierce the object. The punches are adapted for piercing an osmotic drug dispensing vehicle. The piercing means are integral to the punches. They are moved from a sheathed to an unsheathed position by compressive force from punch actuators. Being integral with the punches, the piercing means are not capable of motion or stasis independent of the motion of the punches.

U.S. Patent No. 3,146,169 describes a tablet comprising a medicated portion and a non-medicated inert portion of sublimed sulfur, plastic, bone phosphate, barium sulfate, wax, calcium silicate and or aluminum silicate which covers part but not all of the surface of the medicated portion. The function of the inert portion is to expose to the gastric fluids only a portion of the surface of the medicated portion (through a single hole in the inert portion) so as to slow the rate of release relative to a conventional tablet and maintain the rate of release constant. The tablet is made by feeding the space between the upper and lower punch faces of a compression coating machine successive batches of material; first,

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granules of inert material; second, a preformed core of the medicated material; and third, more granules of the inert material. The upper punch face is provided with a protrusion so that when the punch faces are brought together the inert material is compressed around the inner medicated core in the form of a layer provided with a hole made by the protrusion on
5 the upper punch face. The protrusion is pointed and forms a single hole in the medicated portion as well as the inert portion.

U.S. Patent No. 5,551,856 describes an apparatus for connecting an assembly of three concentrically aligned movable punches which are independently actuated by hydraulic means to a main body of a pressing machine.

10 In view of the foregoing, there is a need for a versatile solid dosage form that reduces contact between the mucosa lining the gastrointestinal tract and a solid drug contained in the dosage form and equipment and a process for producing such a dosage form.

SUMMARY OF THE INVENTION

15 One object of the invention is to provide a novel solid dosage form for oral administration to a patient wherein the active ingredient is contained in a core tablet that is sheathed in a compressed annular body of powder or granular material formed around the core tablet by compression.

Another object of the invention is to provide a solid dosage form for oral
20 administration to a patient that reduces contact between the mucosa lining the gastrointestinal tract and a solid drug contained in the dosage form. In satisfaction of this object there is provided a preferred embodiment of the solid dosage form in which the core tablet is recessed in the annular body to shield it from contact with the mucosa lining the
25 || gastrointestinal tract. The solid dosage form is well suited for oral delivery of ulcerative || active ingredients like bisphosphonates and NSAIDs. In an especially preferred dosage form embodiment, the annular body has opposed annular faces that are aligned substantially coaxially with recessed opposing surfaces of the core tablet. The opposed surfaces of the core tablet are substantially exposed to the external environment and drug release occurs from the exposed surfaces.

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In a second dosage form embodiment, which is suitable for use with non-ulcerative drugs, the opposed surfaces of the core tablet are not recessed. Rather, they are flush with the annular faces of the annular body.

Another object of the invention is to provide a toolset that can be used with
5 commercially available tableting presses to make the solid dosage forms of the invention. The toolset comprises a generally columnar punch having a contact face for pressing against a powder or granular material. The contact face has a protrusion near its center if the upper punch is to be used to make a compacted dosage form with a recessed core tablet. The toolset further comprises a punch assembly comprising an annular punch and a
10 core rod slidably engageable with the annulus of the annular punch and capable of movement between a retracted position and an extended position, the core rod being biased in an extended position when the toolset is in use.

Yet another object of the invention is to provide a process for making the solid dosage forms of the invention. In its particulars, the process comprises filling an annular cavity
15 defined by a die bore, the core rod and the contact face of the annular punch with a powder or granular material, positioning a core tablet atop the tip of the core rod and advancing the columnar punch into the die bore.

The columnar punch pushes the core tablet into the die bore against the bias force exerted by the core rod. If the columnar punch is equipped with a protrusion, the
20 protrusion pushes the core tablet into the die. Otherwise, the contact surface of the columnar punch pushes the core tablet into the die bore. As the core tablet is pushed into the die bore, the core rod retracts against the bias force. Meanwhile, the action of the columnar punch compresses the powder or granular material into an annular body around the core tablet.

25 The process further comprises withdrawing at least one of the punches from the bore and ejecting the finished dosage form, such as withdrawing the columnar punch and advancing the annular punch to eject the dosage form.

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BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows sectional perspective, side and top down views of a solid dosage form with a recessed core tablet of active ingredient in a compressed annular body of powder or granular material in accordance with the invention.

5 FIG. 2 is a perspective view of a single station tableting press shown with the toolset installed.

FIG. 3 is a sectional side view of the columnar punch and punch assembly.

FIGs. 4a-4e are sectional side views depicting stages in a cycle of operation from delivery of powder or granular material to ejection of a finished tablet at a tableting station
10 equipped with a toolset in accordance with the invention.

FIG. 5 is a plot of the average rate of alendronate excretion in urine of humans who had taken a dosage form in accordance with the present invention containing 70 mg monosodium alendronate and a prior art 70 mg monosodium alendronate dosage form.

15 **DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The present invention provides a novel solid dosage form, as well as tooling and a process for producing the novel dosage form. Preferred embodiments of the invention are well suited for the administration of ulcerative drugs. As used in this disclosure, the term
20 "ulcerative" in reference to an active pharmaceutical ingredient, drug or excipient means that when the drug or excipient is contacted as a solid with the mucosa lining at least a portion of the gastrointestinal tract it causes erosive damage. Alendronate, other bisphosphonates and NSAIDS that non-selectively inhibit the COX-1 and COX-2 enzyme are ulcerative drugs.

The novel dosage form comprises a core tablet containing an active pharmaceutical
25 ingredient sheathed in an annular body comprised of compressed powder or granular material. The core tablet has first and second opposed surfaces and a circumferential surface. "Sheathing" means that the annular body encircles the core tablet and is in contact with the core tablet about its circumferential surface, but leaves opposed surfaces of the core tablet substantially exposed. The core tablet contains at least one active
30 pharmaceutical ingredient, but otherwise its formulation is not critical to the invention. The core tablet can be formulated for any desired release profile, such as immediate

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release, delayed release, burst or pulsed release, sustained or zero order release. The annular body can be formulated to achieve any desired purpose, such as gastric retention, ease of swallowing, taste masking and control of the rate of drug release from the core tablet. The annular body also can contain or be coated with a co-active ingredient.

- 5 The type of drug to be delivered also is not an essential element of the invention. The terms “drug” and “active pharmaceutical ingredient” broadly include any biologically, physiologically, or pharmacologically active the agent. Active pharmaceutical ingredients that can be administered in the compressed dosage form of the present invention include
- 10 adrenergic receptor agonists and antagonists; muscarinic receptor agonists and antagonists; anticholinesterase agents; neuromuscular blocking agents; ganglionic blocking and stimulating agents; sympathomimetic drugs; serotonin receptor agonists and antagonists; central nervous system active drugs such as psychotropic drugs, antipsychotic drugs, antianxiety drugs, antidepressants, antimanic drugs, anesthetics, hypnotics, sedatives, hallucinogenic drugs and antihallucinogenic drugs; antiepileptic drugs; antimigraine drugs;
- 15 drugs for treatment of Parkinson’s, Alzheimer’s and Huntington’s disease; analgesics; antitussive agents; antihistaminic drugs; H_1 , H_2 , and H_3 receptor antagonists; bradykinin receptor antagonists; antipyretic agents; antiinflammatory agents; NSAIDs; diuretics; inhibitors of Na^+ - Cl^- symport; vasopressin receptor agonists and antagonists; ACE inhibitors; angiotensin II receptor antagonists; renin inhibitors; calcium channel blockers;
- 20 β -adrenergic receptor antagonists; antiplatelet agents; antithrombic agents; antihypertensive agents; vasodilators; phosphodiesterase inhibitors; antiarrhythmic drugs; HMG CoA reductase inhibitors; H^+ , K^+ -ATPase inhibitors; prostaglandins and prostaglandin analogs; laxatives; antidiarrheal agents; antiemetic agents; prokinetic agents; antiparasitic agents such as antimalarial agents, antibacterial agents, drugs for treatment of
- 25 protozoal infections and antihelminthic drugs; antimicrobial drugs such as sulfonamides, quinolones, β -lactam antibiotics, aminoglycosides, tetracyclines, chloramphenicol and erythromycin; drugs for treatment of tuberculosis, drugs for treatment of leprosy; antifungal agents; antiviral agents; antineoplastic agents; immunomodulators; hematopoietic agents; growth factors; vitamins; minerals; anticoagulants; hormones and
- 30 hormone antagonists such as antithyroid drugs, estrogens, progestins, androgens,

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adrenocortical steroids and adrenocortical steroid inhibitors; insulin; hypglycemic agents; calcium resorption inhibitors; glucocorticoids; retinoids and heavy-metal antagonists.

The annular body can be formed of any powdered or granular pharmaceutically acceptable excipients and can itself include a pharmaceutically active ingredient. In particular, it may be mentioned that diluents, binders, disintegrants, glidants, lubricants, flavorants, colorants and the like can be included in the annular body. Powdering and granulation with conventional excipients and the techniques for forming compressed bodies therefrom with given characteristics in terms of friability, hardness and freedom from capping is well within the knowledge of those skilled in the art of tableting.

Preferred excipients for forming the annular body include hydroxypropyl cellulose (*e.g.*, Klucel™), hydroxypropyl methylcellulose (*e.g.* Methocel™), microcrystalline cellulose (*e.g.*, Avicel™), starch, lactose, sugars, polyvinylpyrrolidone (*e.g.*, Kollidon™, Plasdone™) and calcium phosphate.

In an especially preferred compressed dosage form illustrated in FIG. 1, core tablet 1 containing the active pharmaceutical ingredient is recessed in the annular body 2, which is composed of non-ulcerative pharmaceutical excipients. The “recessed” tablet is especially well suited for oral delivery of ulcerative drugs. It reduces the incidence of pill esophagitis and contact gastritis by localizing the ulcerative drug in a core tablet that is shielded from contact with the mucosa lining the gastrointestinal tract. The drug is shielded because the core tablet is recessed. Recessing the core tablet does not significantly alter the release profile of the core tablet because a sizable portion of the surface of the core tablet is in fluid communication with the environment. In contrast, in coated or encapsulated dosage forms, the coating or capsule must be breached by gastric fluid before the drug is released. In the present invention, the outer contour of the dosage form protects the mucosa lining the gastrointestinal tract without interrupting fluid communication between the core tablet and the environment.

Exemplary of drugs that can be advantageously delivered using the preferred recessed dosage form of this invention are monosodium alendronate monohydrate, monosodium alendronate trihydrate, sodium etidronate, sodium risedronate, pamidronate, aspirin, ibuprofen, naproxen, fenoprofen, ketoprofen, oxaprozin, flubiprofen, indomethacin,

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sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, diclofenac, piroxicam, meloxicam, tenoxicam, phenylbutazone and oxyphenbutazone.

Turning again to FIG. 1, core tablet 1 has opposed first and second surfaces 3 and 4 and an outer circumferential surface 5 extending between the opposed surfaces. Core tablet 1 is preferably cylindrical or disk shaped for ease of manufacture, but need not be so. In a dosage form for administration to humans, the maximum distance across either of the opposed surfaces 3 or 4 is preferably from about 2 mm to about 12 mm, more preferably from about 4 mm to about 7 mm, most preferably about 5 mm. Opposed surfaces 3 and 4 can be flat, concave or convex and are preferably flat for bearing modest axial compression forces exerted by flat pressing surfaces during formation of the annular body about the core tablet.

In outer contour, annular body 2 is preferably cylindrically shaped, but it can have any cross section, such as oval, elliptical or oblong. The outer diameter is preferably of from about 5 mm to about 15 mm, more preferably of from about 7 mm to about 12 mm, most preferably about 9 mm. The inner diameter can be any size up to about 2 mm less than the outer diameter. A narrow inner diameter less than 2 mm may slow release of the drug if an excipient in the annular body swells upon contact with gastric fluid. However, in some embodiments, a lower limit 0.5 mm may still be useful. Preferably, the inner diameter is 3 mm or greater.

Annular body 2 has opposed first and second annular faces 6 and 7, an outer circumferential surface 8 extending between the annular faces from their outer edges, and an inner circumferential surface 9 extending between the annular surfaces from their inner edges, thus defining an annulus.

As best seen in side view (FIG. 1B), inner circumferential surface 9 of annular body 2 consists of three longitudinal (axial) segments. First and second segments 10 and 11 are terminal and do not contact the sides of the core tablet. They are separated by an internal third segment 12 that contacts the outer circumferential surface 5 of core tablet 1.

Opposed surfaces 3 and 4 of the core tablet are therefore recessed from annular faces 6 and 7 of the annular body. Opposed surfaces 3 and 4 are preferably recessed from about 0.5 mm to about 4 mm, more preferably about 1.5 mm relative to the annular faces 6 and 7 of the annular body (said recessed distance corresponding to the length of the corresponding

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terminal segment). The recess depth of surfaces 3 and 4 can be the same or it can be different.

By recessing the drug-containing core tablet, any contact between the dosage form and the gastrointestinal mucosa occurs with a surface of the annular body formed of non-ulcerative excipients, and optionally one or more non-ulcerative co-active ingredient, rather than with the solid ulcerative active ingredient. However, one or both of opposed surfaces 3 and 4 can be flush with annular faces 6 and 7 of the annular body without deleterious effect when the dosage form of the present invention is used to administer non-ulcerative drugs.

To better apprehend the preferred recessed dosage form embodiment of the invention, it is useful to conceive of surface 3 of the core tablet and first longitudinal segment 10 as defining a first void 13. Likewise, surface 4 of the core tablet and second longitudinal segment 11 define a second void 14. Voids 13 and 14 fill with gastric fluid when the dosage form is immersed in gastric fluid after reaching the stomach. Gastric fluid passes through the voids to contact the core tablet and the drug leaves through the voids after it is dissolved. Voids 13 and 14 are preferably from about 0.5 mm to about 10 mm, more preferably from about 3 mm to about 6 mm and most preferably about 4.5 mm in width (measured parallel to first or second opposed surfaces). Drug release, therefore, does not occur by an osmotic mechanism such as occurs with pierced dosage forms made using the apparatus of U.S. Patent No. 5,071,607. Rather, in a large still fluid environment, drug concentration drops off roughly isotropically and exponentially by diffusion. In contrast, osmotic release of the drug product would produce a streaming flow that can cause locally high concentrations of the drug and osmotic agents at considerable distance from the tablet. Osmotic streams highly concentrated in an ulcerative drug are potentially irritating to the mucosa, just like the solid drug, particularly if the tablet is lodged in a fold in the gastrointestinal wall.

Opposed surfaces 3 and 4 of the core tablet are preferably substantially exposed, *i.e.* are not substantially covered by the annular body. "Substantially exposed" means that less than about 50% of each of the opposed surfaces is concealed or hidden from visual inspection by the annular body. A portion of opposed surfaces 3 and 4 can be concealed by the annular body because of differences between the diameter and shape of the core tablet

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and the diameter and shape of certain pressing portions of the tooling used to compress the annular body, as will become apparent from consideration of the description of the tooling aspect of the invention. Such differences may result in inner segment 12 being offset from terminal segments 10 and 11, which, themselves, can have different longitudinal cross sections, *e.g.* have different diameters, as depicted in FIG 1. Alternatively, the cross section of the annulus defined by inner circumferential surface 9 can be uniform throughout its length. Although a portion of opposed surfaces 3 and 4 can be concealed by the annular body that is not necessarily the case.

The solid dosage forms with a drug-containing core tablet sheathed in a compressed annular body of non-ulcerative excipients can be produced using a novel toolset that constitutes a second aspect of the invention.

The toolset can be used in conjunction with conventional tablet presses such as rotary presses and reciprocating presses or with presses that have been specially designed and manufactured. Examples of commercially available rotary presses are the Manesty Express 25, the Kilian RUD or RTS series and comparable equipment. Examples of commercially available reciprocating presses are the Manesty F3 and comparable equipment made by Stokes, Kilian and Key Industries.

The principle elements of the toolset are a columnar punch and a punch assembly comprising an annular punch having an annulus (or bore), a core rod slidably engageable within the annulus of the annular punch, wherein the core rod is capable of movement between a retracted position and an extended position, the core rod being biased in the extended position. The columnar punch and punch assembly are sized and shaped to fit into the die bore of a rotary or reciprocating tablet machine.

The toolset is well adapted for use with conventional single station tablet presses in which opposing upper and lower punches cooperatively compress a powder or granular material within a die. Referring to FIG. 2, single station presses are provided with a horizontal die table 15 having an aperture for receiving a die 16 and associated gripping means for locking the die into position. Dies for such presses customarily have opposed flat surfaces with a centrally located bore 17 having a highly polished wall surface extending from surface to surface and a circumferential locking groove 18 for engaging the gripping means. The bore serves as a receptacle for receiving powder or granular material

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to be compressed when the lower punch is partially inserted. The rims of the bore are customarily chamfered to help guide the punches into the bore. The bore's cross section determines the size and shape of the finished tablet in cross section. The quantity of material and pressure of compression determine the tablet's height. The bore can be
5 cylindrical, but also can be any other shape.

In operation, the bore is filled with material and the upper punch is inserted into the bore and pressed against the material under high pressure thereby compressing the powder or granulated material into a tablet between the pressing, or contact, surfaces of the punches.

10 Together, the wall of the bore and the contact surfaces of the upper and lower punches define a mold that determines the size and surface contours of the final product. The final product can have any external contour by selection of appropriate bore shape and contact face contour.

After compression, the upper punch is withdrawn and the lower punch is advanced to
15 eject the tablet.

The upper and lower punches are advanced and withdrawn by independently actuated upper and lower reciprocating rams 19 and 20. Customarily, single punch presses are also provided with a stationary mounting point 21 below the die table coaxial with the aperture.

A toolset of this invention adapted for use in a single station press comprises a
20 columnar punch and a punch assembly comprising a collar, core rod and annular punch.

Referring now to FIG. 3, columnar punch 22 can be of a conventional columnar shape and is provided with locking means, such as locking flat 23 to secure it to the upper reciprocating ram 19 of the tablet press.

Columnar punch 22 includes a contact face 24. Contact face 24 can have any desired
25 contour, *e.g.* standard concave, deep concave, extra deep concave, modified ball or flat. Preferably, the contour of contact face 24 is flat with a beveled edge.

A columnar punch for use in producing a dosage form of the present invention having a recessed core also has a protrusion 25 centrally located on the contact face 24, as illustrated. Preferably, the height of protrusion 25 is from about 0.5 mm to about 4 mm,
30 more preferably about 1.5 mm. The shape of the protrusion is preferably cylindrical or tapered cylindrical but can also be oval, ellipsoid, oblong or any other shape desired. The

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protrusion is preferably cylindrical and has a flat raised surface 26. Protrusion 25 preferably has a diameter of from about 3 mm to about 7 mm, more preferably about 4.5 mm. In other embodiments, particularly suited to use when non-ulcerative active pharmaceutical ingredients are to be administered, protrusion 25 is absent.

5 Punch assembly 27 comprises collar 28, core rod 29 slidably engaged with collar 28 and annular punch 30 slidably engageable with core rod 29.

Collar 28 is provided with mounting means, such as external threads 31 around its circumference for mounting to stationary mounting point 21 located below the die table. As illustrated, the distal end 32 of collar 28 relative to the die table when installed, has a
10 gripping section (shown with optional hexagonal cross section) for gripping by a wrench for mounting to stationary mounting point 21. At the proximal end 33 of the collar 28 relative to the die table when installed, the annulus is dimensioned to receive and guide the core rod 29.

Away from the proximal end of the collar, the diameter of the annulus is substantially
15 greater than that of the core rod to provide a housing 34 for a biasing means such as spring 35. The coils of spring 35 encircle the core rod. Although a coil spring 35 is a preferred biasing means, biasing can be accomplished by other means, such as a stack of Belleville washers or an elastic insert.

Spring 35 or other biasing means engages retaining ring 36 mated to core rod 29.
20 Retaining ring 36 can be mated to the core rod by clamping engagement with a circumferential groove 37 in the rod. The retaining ring can be a conventional C-clip which engages the groove, or it can be a clamp or any other structure against which the biasing means can exert a biasing force and which is restrained from movement relative to core rod 29 in a direction parallel to the long axis of the core rod.

25 As illustrated, an annular locking bolt 38 engages internal threads 39 at the distal end of collar 32. The bore 40 through locking bolt 38 is dimensioned to receive and, in conjunction with the annulus at the proximal portion of the collar, to restrain motion of core rod 29 to axial movement. Locking bolt 38 also retains and can compress the biasing means. Core rod 29 is biased in the direction of the die table when the collar is installed on
30 stationary mounting point 21 and is retained in slidable engagement with collar 28 by retaining ring 36 and locking bolt 38. The height of rod tip 41 is adjusted by advancing or

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retracting collar 28 relative to stationary mounting point 21, *e.g.* by rotating the collar when in threaded engagement with the stationary mounting point.

Core rod 29 can vary in diameter along its length. A preferred diameter of rod tip 41 is from about 0.5 mm to about 10 mm, more preferably about 4.5 mm. However, for
5 rigidity, the core rod should be thicker, preferably from about 4 mm to about 12 mm throughout most of its length, more preferably about 9 mm. The rod can taper gradually from a narrow diameter at the tip to a larger shank diameter or it can change abruptly at a shoulder 42.

The core rod can be of two-piece construction. For instance, the core rod tip 41 could
10 be adapted to attach to the core rod by providing external threads at its lower end and a socket with internal threads at the upper end of the core rod, or vice versa. A two-piece construction allows the core rod tip to be replaced if it is damaged or if a core rod tip of a different shape is desired. The core rod tip can have any desired diameter or shape.

Punch assembly 27 further comprises annular punch 30. Annular punch 30 is
15 provided with means for attaching to lower reciprocating ram 20, such as locking flat 43. The bore 44 through annular punch 30 is dimensioned to receive and surround core rod 29 while permitting axial movement of annular punch 30 independent of the core rod. The bore through annular punch 30 can vary in diameter along the length of the punch providing an annular flange 45 for engagement with shoulder 42 on the core rod.
20 Engagement of flange 45 with shoulder 42 prevents annular punch 30 and collar 28 from abutting each other during handling and installation. Annular punch contact surface 46 presses against the powder or granular material during compression. Contact face 46 can have any desired contour, *e.g.* standard concave, deep concave, extra deep concave, modified ball or flat. Preferably contact face 46 is flat with a beveled edge for ease of
25 ejection of the finished tablet.

The columnar punch, annular punch, core rod and collar are preferably made of metal, more preferably steel, most preferably stainless steel.

In the final dosage form with recessed core tablet, the depth of first void 13 (FIG. 1) is determined by the height of protrusion 25. The depth of second void 14 is determined by
30 the fill depth, strength of the bias on the core rod, the compressibility of the material and the thickness of the core tablet. These parameters can be adjusted by routine

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experimentation to control the depth of second void 14, which is suitably commensurate with the depth of first void 13.

In a second dosage form embodiment, either one or both of opposed surfaces 3 and 4 of the core tablet are flush with the annular faces 6 and 7 of the annular body 2. This alternative embodiment can be produced by using a columnar punch as previously described but lacking a protrusion 25. Surface 3 will generally be flush with annular face 6 if the columnar punch has a flat contact face. Whether the opposed surface 4 is flush with annular face 7 will depend on the fill depth, compressibility of the powder or granular material and thickness of the core tablet, which factors can be adjusted by routine experimentation to yield a dosage form with surface 4 recessed the desired distance relative to annular face 7.

To further illustrate the invention and the operation of the toolset, a cycle of operation will now be described. The cycle of operation is embodied in a process that constitutes a third aspect of the invention.

The cycle of operation is first illustrated on a single station press. The cycle begins with the first action that occurs after ejection of the tablet formed in a previous cycle. Referring now to FIG. 4a, feed shoe 47 moves laterally over the die bore while the annular punch 30 is in an advanced position such that contact surface 46 is substantially flush with the top surface of the die. In so doing, the feed shoe sweeps a finished tablet from atop the annular punch toward a chute leading to a receptacle where the tablets are collected. Annular punch 30 is retracted while the tip 41 of core rod 29 remains flush with the die surface (FIG. 4b). Retraction of the annular punch causes an annular cavity to form into which particles of the powder or granular material are fed from the feed shoe by gravity and/or pressure differential. Once the cavity is filled, the feed shoe is shifted away from the die bore.

Pre-compressed core tablet 1 is positioned atop the core rod using any conventional apparatus for producing tablets with a compressed coating such as that of a Kilian RUD press (FIG. 4c). The positioning means forms no part of the invention and has been omitted for clarity.

Columnar punch 22 is advanced by upper reciprocating ram 19 (FIG. 4d). As columnar punch 22 approaches the bore, the raised surface 26 of protrusion 25 presses

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upon core tablet 1. As columnar punch 22 enters bore 17, core tablet 1 is pushed into the bore by the protrusion against the biasing force exerted on core rod 29. Continued movement of columnar punch 22 into the die bore compresses the powder or granular material into an annular body around the core tablet. Strong compressive forces can be exerted on the powder or granular material without breaking the core tablet because the core tablet travels into the bore before the powder or granular material is fully compressed.

Those skilled in the art may also appreciate that protrusion 25 could be replaced with a core rod in the columnar punch that is biased toward an extended position so that the tip of the rod would press against core tablet 1 during compression. Such a core rod for the columnar punch would not necessarily be attached to a stationary mounting point on the press. It would be biased with greater force than core rod 29 so that pressure exerted by the columnar punch would push the core tablet into the bore against the resistance of the core rod.

After the powder or granular material is compressed, the columnar punch is withdrawn. Either concurrently or subsequently, annular punch 30 is advanced by lower reciprocating ram 20 to a position such that contact face 46 is substantially flush with the upper surface of the die to elevate the finished tablet above the die where it can be swept from the die table in a subsequent cycle of operation (FIG. 4e). Meanwhile, the core rod is biased back to its original position flush with the die surface.

The toolset is well adapted for use in a rotary tablet press. The cross-sectional dimension and shape of the columnar punch, and the dimensions and shape of the protrusion (if present) are the same as in a punch adapted for use in a reciprocating tablet press. The other dimensions of the toolset are generally dictated by the dimensions and layout of a particular tableting press. These dimensions can be readily determined by those skilled in the art. The cross-sectional dimensions and shape of the annular punch and of the core rod are the same as in a punch adapted for use in a reciprocating tablet press, again with other dimensions being dictated by the dimensions and layout of a particular tableting press. These dimensions can be readily determined by those skilled in the art. In addition, the punches include conventional bearing surfaces at the end distal to their contact surfaces for engaging the cams and rollers that control their motion along the axis

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of the die bore, such as those shown in the patents that are incorporated by reference below.

In an annular punch for use in a rotary machine, the core rod biasing means preferably is housed in the annular punch and includes a means for adjusting the degree of extension
5 of the core rod and/or the bias, such as a set screw or similar device.

Conventional rotary tablet presses are well known in the art. Some rotary presses and improvements related thereto are described in U.S. Patents Nos. 5,462,427, 5,234,646, 5,256,046 and 5,635,223, which are incorporated herein by reference in their entirety. Rotary presses have a moving die table that rotates around a vertical axis. Mounted above
10 and below the die table are upper and lower punch carriers that rotate synchronously with the die table. The punch carriers can be generally drum shaped bodies of about the same diameter as the die table or they can have arms that extend outward from a lesser diameter ring. The punch carriers are provided with a plurality of vertical holes or slots at regular intervals around their circumference or through the ends of the arms. When the press is in
15 operation, punches are inserted into each slot with their contact faces pointing toward the die table. Each punch has a bearing means at the end opposite the contact face. The bearing means engage stationary cams and rollers which control the vertical motion of each punch during a cycle of operation. The cams and rollers are arranged such that in a cycle of operation, a powder or granular material is fed into a die while the lower punch is
20 inserted into the die. Pressure is applied to the powder or granular material to produce a compressed body. After compression, one or more of the punches is removed from the die and the dosage form is released. Rotary presses are especially suited for high volume production because they typically contain numerous punch and die sets operating simultaneously.

25 A cycle of operation using the toolset of this invention adapted for use in a rotary press will now be described. As the die table rotates, one of the dies passes under a fill shoe or force feeder. While the die is passing underneath the shoe or feeder, the annular punch is withdrawn by the cam. The core rod remains in an extended position, up to the upper die face. The annular space left by withdrawal of the annular punch is filled with
30 powder or granulate. At the next station, a core tablet is inserted onto the tip of the core rod by conventional means, such as those used in "press coat" machines like the Kilian

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RUD. The core tablet can be positioned atop the core rod by any method. On further rotation, the die comes to the compression station where the columnar punch with, or without, its protrusion moves downward and pushes the core tablet into the bed of powder or granular material. The force of the columnar punch retracts the core rod against the bias
5 and the powder or granular material is compressed into an annular shape around the core tablet. In the dosage form product, one recess is defined by the height of the protrusion and the other recess is defined by a combination of the factors such as the strength of the bias, the fill depth, the compactability of the powder or granular material and the thickness of the core tablet. After the powder is compressed, the die rotates further to where the
10 columnar punch is withdrawn from the die. Either concurrently or subsequently, the annular punch is raised until it reaches the die face. The core rod rises concurrently to the die face due to the bias. The tablet is swept out of the die by an ejection element and is collected.

While reference has been made to “upper” and “lower” elements in the description of
15 the toolset and process for making solid dosage form according to the invention, the spacial relationships of the elements are determined by the design and construction of the press in which they are used. Use of the terms “upper” and “lower” is not intended to limit the invention to a vertical arrangement of the elements.

Having thus described the present invention with reference to certain preferred
20 embodiments, the invention will now be further illustrated by the following example.

EXAMPLE

This example summarizes a study designed to determine the rate and extent of
25 absorption of alendronate sodium in human subjects upon administration of a solid pharmaceutical dosage form of the present invention (“protected tablet”).

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Materials and Methods

Protected tablets were made as follows.

Tablet Core: 85.4 g of alendronate trihydrate (TEVA Assia Ltd.) and 2.6 g of xylitol (Danisco Sweeteners OY) were granulated with 20 g water in a Diosna (model P1/6) granulator for 3 min. The granulate was dried at 40°C for one hour in a fluidized bed dryer and milled through a 0.8 mm screen. The granulate was blended with 11 g crospovidone NF (BASF Pharma) for five minutes. One gram magnesium stearate NF/EP (Mallinkrodt Inc.) was added and the granulate was further blended for an additional 0.5 minutes. The blend was compressed using a Manesty F3 single punch tablet machine fitted with a 5 mm flat beveled punch. The tablet weight was 94.9 mg \pm 1.0% RSD. The hardness of the core tablets was 3 – 6 kP.

Protected Tablets: A mixture of 94 grams compressible sucrose (Nutab™, DMV International) and 5 grams microcrystalline cellulose (Avicel™ pH102, FMC International) were blended for five minutes. One gram magnesium stearate (NF/EP, Mallinkrodt Inc.) was added and the mixture was blended for another half a minute.

A Manesty f3 single punch tableting machine was fitted with a spring-biased columnar punch and punch assembly constructed in accordance with the present invention. The core rod was designed for a 5 mm round core tablet and the die and punches for the outer tablet were designed to produce a round, 9 mm diameter, flat beveled solid pharmaceutical dosage form. The upper punch had a protrusion of diameter 4.5 mm and 1.2 mm height. The tablet press was operated and the protected tablets were produced. The tablet weight was 474 mg \pm 0.62% RSD and the hardness of the protected tablets was 12 – 15 kP. The alendronate trihydrate content, expressed as alendronic acid was 66.8 mg \pm 1.38% RSD (82.4 mg alendronate trihydrate being equivalent to 70 mg alendronic acid).

The drug-containing inner tablet was recessed from the surface of the annular body by about 1 mm.

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Pharmacokinetic Study

A clinical trial involving twelve (12) human volunteers was conducted to demonstrate the pharmacokinetics of a solid dosage form of the present invention containing 70 mg alendronate. Its pharmacokinetics was compared to that of a commercial 70 mg Fosalan™
5 tablet of the prior art (Merck, Sharpe & Dohme).

Method

The study was a randomized, open-label, 2-treatment, 2 period, 2 sequence crossover design under fasting conditions. Twelve (12) healthy adult male volunteers, 18-55 years of age were the subjects in the study.

10 The study was divided into first and second study periods, each of 36 hours duration, with a 14 day "wash-out" period between the study periods. All subjects who completed both study periods were included in the analysis. Subjects were randomly assigned to two groups. One group was administered alendronate via the protected tablet in the first period and administered control Fosalan in the second period. The order of administration to the
15 second group was reversed.

In both periods, alendronate was administered in the fasted state. A standardized meal was provided 4 hours after administration. Snacks were provided on a standardized schedule that was the same for all subjects in both study periods. Water was provided *ad libitum*. In addition, subjects were encouraged to drink at least 200 ml of water at regular
20 intervals during each study period.

The bioavailability of alendronate was determined by measuring the cumulative levels of alendronate excreted in the urine over a 36 hour period following oral ingestion of the test and control tablets (hereafter " Ae_{0-36} "). An initial ($t = 0$) urine sample was taken immediately after administration. Urine samples were taken at 11 regularly scheduled
25 points in time over the 36 hour test period. All urine samples were analyzed for alendronate using a validated HPLC-FLR assay.

Results

The main pharmacokinetic parameters obtained from the analyses of urine samples are collected in Table 1.

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Table 1: Pharmacokinetic Parameters

Parameter	Administration via Protected Tablet			Administration via Fosalan (control)		
	Mean	± SD	CV (%)	Mean	± SD	CV (%)
Ae_{0-36} (μg)	113.6	77.2	67.9	102.6	36.8	36.8
R_{max} (μg/h)	37.9	19.9	51.5	31.7	11.8	38.3
T_{max} (h)	1.4	0.9	---	1.4	0.9	—

A comparison of the pharmacokinetic parameters of the dosage form in accordance with this invention with the pharmacokinetic parameters of the prior art dosage form is provided in Table 2.

Table 2. Comparison of Pharmacokinetics of the Protected Tablet to Prior Art

	Ae_{0-36} (mg)	R_{max} (mg/h)
Geometric Mean of Ratio	0.99	1.12
90% Geometric C. I.	75.31% to 128.79%	93.98% to 135.01%
Intra-subject C.V.	37.48%	24.85%

By reference to Tables 1 and 2, and FIG. 5, one can see that alendronate administered via the solid dosage form of the present invention gives essentially the same pharmacokinetic results as administration via Fosalan. The total amount of the alendronate excreted into urine over 36 hours is essentially the same for both treatments with the maximum rates of excretion (parallel to C_{max} in a pharmacokinetic study of plasma levels of drug) also close.

The profile of excretion into urine was similar for all subjects and in both treatments. The majority of the subjects had their maximum rate of excretion (R_{max}) between one and two hours. For five of the subjects, the R_{max} occurred earlier than 1 hour after administration when they took Fosalan. Four of the subjects experienced a R_{max} in less than an hour when they took the protected tablet. One of the subjects had an R_{max} in the third hour when he took Fosalan while two of the subjects had a R_{max} in the third hour when they took the protected tablet.

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The total amount of excreted alendronate ranged from 36.9 μg to 158.6 μg when Fosalan was administered and from 30.1 μg to 284.4 μg when the solid oral dosage form of the present invention was administered. In only two subjects was there a greater than two fold difference between the total amount of excreted alendronate between the two
5 treatments. Another subject excreted a very low amount of alendronate regardless of how the alendronate was administered.

The bioavailability of alendronate administered via the novel solid dosage form of the present invention is equivalent to that of alendronate administered by dosage forms of the prior art. However, the dosage form of the prior art does not provide any protection against
10 contact of the alendronate with the mucous membranes of the esophageous and stomach while the bioequivalent novel dosage form of the present invention affords such protection.

Having thus described the invention with reference to certain preferred embodiments, other embodiments will be apparent from this description to those skilled in the art to which the invention pertains. It is intended that the specification is considered exemplary
15 only, with the scope and spirit of the invention being indicated by the claims which follow.

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CLAIMS

What is claimed is:

1. A solid pharmaceutical dosage form for oral administration to a patient comprising a core tablet containing an active pharmaceutical ingredient sheathed in an annular body of compressed powder or granular material formed by compression around the core tablet.
2. The solid pharmaceutical dosage form of claim 1 wherein the core tablet is recessed.
3. The solid pharmaceutical dosage form of claim 2 wherein the active pharmaceutical ingredient is released into the annulus of the annular body.
4. The solid pharmaceutical dosage form of claim 3 wherein the active pharmaceutical ingredient is ulcerative.
5. The solid pharmaceutical dosage form of claim 4 wherein the active pharmaceutical ingredient is a bisphosphonate or NSAID.
6. The solid pharmaceutical dosage form of claim 5 wherein the active pharmaceutical ingredient is selected from the group consisting of monosodium alendronate monohydrate, monosodium alendronate trihydrate, sodium etidronate, sodium risedronate, pamidronate, aspirin, ibuprofen, naproxen, fenoprofen, ketoprofen, oxaprozin, flubiprofen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, diclofenac, piroxicam, meloxicam, tenoxicam, phenylbutazone and oxyphenbutazone.

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7. The solid pharmaceutical dosage form of claim 6 wherein the active pharmaceutical ingredient is monosodium alendronate monohydrate.
8. The solid pharmaceutical dosage form of claim 6 wherein the active pharmaceutical ingredient is monosodium alendronate trihydrate.
9. The solid pharmaceutical dosage form of claim 2 wherein the core tablet is recessed at least from about 0.5 mm to about 4 mm.
10. The solid pharmaceutical dosage form of claim 1 wherein the annular body contains a co-active ingredient.
11. The solid pharmaceutical dosage form of claim 1 wherein the powder or granular material includes a pharmaceutical excipient selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, starch, lactose, sugars, polyvinylpyrrolidone and calcium phosphate.
12. The solid pharmaceutical dosage form of claim 1 wherein:
 - a) the core tablet has a contour including opposed first and second surfaces and an outer circumferential surface extending therebetween,
 - b) the annular body has a contour and orientation with respect to the core tablet wherein first and second opposed annular faces align substantially coaxially with the opposed surfaces of the core tablet, an outer circumferential surface extends from the outer edges of the annular faces and an inner circumferential surface extends from the inner edges of the annular faces.

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13. The dosage form of claim 12 wherein the distance across each of the opposed surfaces of the core tablet is from about 2 mm to about 12 mm.
14. The dosage form of claim 13 wherein the distance across each of the opposed surfaces of the core tablet is from about 4 mm to about 7 mm.
15. The solid pharmaceutical dosage form of claim 12 wherein the core tablet is recessed in the annular body such that the outer circumferential surface of the core tablet engages a segment of the inner circumferential surface of the annular body, and the opposed surfaces of the core tablet are substantially exposed and are recessed from the annular faces of the annular body.
16. The solid pharmaceutical dosage form of claim 15 wherein the opposed surfaces of the core tablet are recessed about 0.5 mm to about 4 mm from the annular faces of the annular body.
17. The dosage form of claim 15 wherein the inner circumferential surface of the annular body consists of a first and second terminal segment and one internal segment, further wherein the first terminal segment and the opposed first surface of the core tablet define a first void and the second terminal segment and the opposed second surface of the core tablet define a second void and further wherein the distance across each of the voids is from about 0.5 to about 10 mm.
18. The dosage form of claim 17 wherein the distance across each void is from about 3 mm to about 6 mm.
19. The dosage form of claim 1 wherein the core tablet is in the shape of a disk or cylinder.

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20. A toolset for producing a solid pharmaceutical dosage form comprising a core tablet sheathed in a compressed annular body of powder or granular material, the toolset comprising:
- a) a columnar punch, and
 - b) a punch assembly comprising an annular punch and a core rod slidably engageable with the annulus of the annular punch, wherein the core rod is capable of movement between a retracted position and an extended position and wherein the core rod is biased in an extended position.
21. The toolset for producing a solid pharmaceutical dosage form of claim 20 further comprising a die with a bore therethrough wherein the extent of movement between the retracted and extended positions is approximately equal to or less than the thickness of the die.
22. The toolset of claim 20 wherein the columnar punch has a contact face with a centered protrusion.
23. The toolset of claim 20 adapted for use in a press having a die table for mounting a die with a bore therethrough such that the axis of the bore is normal to the die table, a first actuated reciprocating ram movable along the axis of the bore and a second actuated reciprocating ram on the opposite side of the die table from the first actuated reciprocating ram movable along the axis of the die bore independently of the first ram, wherein:
- a) the columnar punch is adapted for mounting to one of the reciprocating rams of the press, and has an end sized to be received in the die bore,
 - b) the annular punch is adapted for mounting to the other of the reciprocating rams of the press and has an end sized to be received in the die bore, and

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- c) the punch assembly further comprises a collar adapted for mounting to a fixed point on the press coaxially with the die bore and wherein the core rod is slidably engaged within the annulus of the collar and biased by biasing means housed in the collar.

24. The toolset of claim 20 adapted for use in a press having:

- a generally planar and circular die table capable of rotation about an axis normal to the plane and having a plurality of bores therethrough around its circumference at regular intervals,
- a first punch carrier mounted on one side of the die table and a second punch carrier mounted on the other side of the die table, each punch carrier rotating about the axis synchronously with the die table and provided with a plurality of vertical holes or slots for receiving punches, each hole or slot being in registry with a bore through the die table,
- means for controlling the motion of punches in the direction of the axis, wherein:
 - a) the columnar punch is adapted for slidable engagement with the holes or slots in the first punch carrier and has an end sized to be received in a bore,
 - b) the annular punch is adapted for slidable engagement with the holes or slots in the second punch carrier and has an end sized to be received in a bore, and
 - c) the core rod is capable of independent motion relative to the annular punch.

25. A process for producing a solid pharmaceutical dosage form comprising forming an annular body of powder or granular material around a core tablet by compression.

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26. The process for producing a solid pharmaceutical dosage form of claim 25 wherein forming the annular body comprises:
- a) filling an annular cavity with the powder or granular material, the annular cavity being defined by:
 - i) the bore of a die,
 - ii) an annular punch partially inserted into the bore from one side,
 - iii) a core rod in an extended position wherein it extends through the bore and the annular punch with its tip substantially flush with the surface of the die on the side opposite the annular punch, wherein the core rod is movable between the extended position and a retracted position wherein the tip is inside the bore, and further wherein the core rod is biased in the extended position,
 - b) placing the core tablet at the tip of the core rod, and
 - c) advancing a columnar punch toward the bore from the side of the die opposite the annular punch, thereby pushing the core tablet into the bore against the bias force on the core rod and causing the core rod to retract, and compressing the powder or granular material around the core tablet, forming the annular body.
27. The process of claim 26 wherein the columnar punch contact face has a centered protrusion.
28. The process for producing a solid pharmaceutical dosage form of claim 26 further comprising withdrawing at least one of the punches from the die bore after advancing the columnar punch toward the bore and ejecting the solid pharmaceutical dosage form from the bore.
29. The process for producing a solid pharmaceutical dosage form of claim 25, which uses a tablet press equipped with the following parts and tooling:

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a die table mounting a die with a bore extending therethrough,
a columnar punch mounted on one side of the die table coaxially with the bore and movable along the axis of the bore with the end proximal to the die table sized to be received into the bore and being terminated with a contact face for pressing against the powder or granular material,

an annular punch mounted on the other side of the die table coaxially with the bore and movable along the axis of the die bore independently of the columnar punch, wherein the end of the annular punch proximal to the die table is sized to be received into the die bore and is terminated with a contact face for pressing against the powder or granular material, and

a core rod slidably engaged within the annulus of the annular punch and aligned coaxially with the die bore, the core rod moveable between a retracted position and an extended position wherein the core rod extends through the die bore with the tip of the rod substantially flush with the surface of the die, the core rod being biased to the extended position by biasing means,

wherein forming the annular body comprises:

- a) filling an annular cavity with the powder or granular material, the annular cavity being defined by the die bore, the core rod in its extended position and the contact face of the annular punch partially inserted into the bore,
- b) placing the core tablet at the tip of the extended core rod,
- c) advancing the columnar punch, whereby the core tablet is pushed into the die bore against the bias force exerted by the core rod biasing means, whereby the core rod at least partially retracts, and whereby the powder or granular material is compressed between the contact faces of the columnar and annular punches, forming the annular body.

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30. The process for producing a solid pharmaceutical dosage form of claim 29 further comprising withdrawing at least one of the punches from the die bore after advancing the columnar punch toward the bore and ejecting the solid pharmaceutical dosage form from the bore.
31. The process of claim 29 wherein the columnar punch contact face has a centered protrusion.
32. The process for producing a solid pharmaceutical dosage form of claim 29
- wherein the die table is horizontal, the columnar punch is above the die table, and the annular punch is below the die table,
- wherein the tablet press is further equipped with a feed shoe for delivering the powder or granular material to the die bore from above and a collar fixedly mounted below the die table coaxially with the die bore, the core rod being slidably engaged within the annulus of the collar and biased by bias means housed in the collar, and
- wherein, the annular cavity is filled from the feed shoe, the columnar punch is withdrawn after the advancing step and the solid pharmaceutical dosage form is ejected from the bore by advancing the annular punch into the bore.
33. The process of claim 32 wherein the annular cavity is filled by placing the feed shoe over the die bore while the annular punch is positioned with its contact face approximately flush with the die surface and then lowering the lower punch to form the cavity and drawing the powder or granular material into the cavity by gravity or pressure differential.
34. The process for producing a solid pharmaceutical dosage form of claim 25 which uses a tablet press equipped with the following parts and tooling:

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a generally planar and circular die table capable of rotation about an axis normal to the plane and having a plurality of bores therethrough around its circumference at regular intervals,

a first punch carrier mounted on one side the die table and a second punch carrier mounted on the other side of the die table, each punch carrier rotating about the axis synchronously with the die table and provided with a plurality of vertical holes or slots, each hole or slot being in registry with a bore through the die table,

a plurality of annular first punches, each slidably engaged within one of the vertical holes or slots of the first punch carrier, each of the first punches having an end proximal to the die table sized to be received into a bore and being terminated with an annular contact face for pressing against the powder or granular material, each of the first punches further having a core rod slidably engaged within the annulus and aligned coaxially with a die bore, the core rod moveable between a retracted position and an extended position wherein the core rod extends through the die bore with the tip of the rod substantially flush with the surface of the die table, the core rod being biased to the extended position by biasing means,

a plurality of second punches, each slidably engaged within one of the vertical holes or slots of the second punch carrier, each of the second punches having an end proximal to the die table sized to be received into a bore and terminated with a contact face for pressing against the powder or granular material,

means for controlling the motion of the punches in the direction of the axis,

wherein forming the annular body comprises:

- a) filling an annular cavity with the powder or granular material, the annular cavity being defined by a die bore, a core rod in its extended position and the contact face of a first punch partially inserted into the bore,
- b) placing the core tablet at the tip of the extended core rod,

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- c) advancing a second punch into the die bore, whereby the core tablet is pushed into the die bore against the bias force exerted by the core rod biasing means, whereby the core rod at least partially retracts, and whereby the powder or granular material is compressed between the contact faces of the first and second punch, forming the annular body.
35. The process for producing a solid pharmaceutical dosage form of claim 34 further comprising withdrawing at least one of the punches from the die bore after advancing the second punch toward the bore and ejecting the solid pharmaceutical dosage form from the bore.
36. The process of claim 34 wherein the second punch contact face has a centered protrusion.
37. The process of claim 34 wherein the annular cavity is filled by rotating the die table under a feed shoe while the first punch is positioned with its contact face substantially flush with the die table surface and then retracting the first punch to form the cavity and drawing the powder or granular material into the cavity by gravity or pressure differential.
38. A solid pharmaceutical dosage form produced by the process of claim 25.

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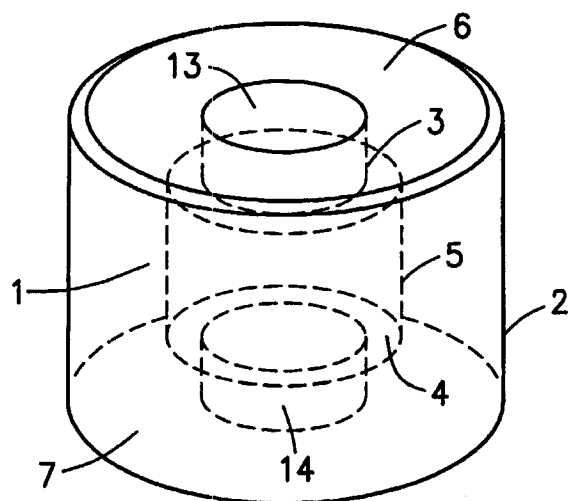


Fig. 1a

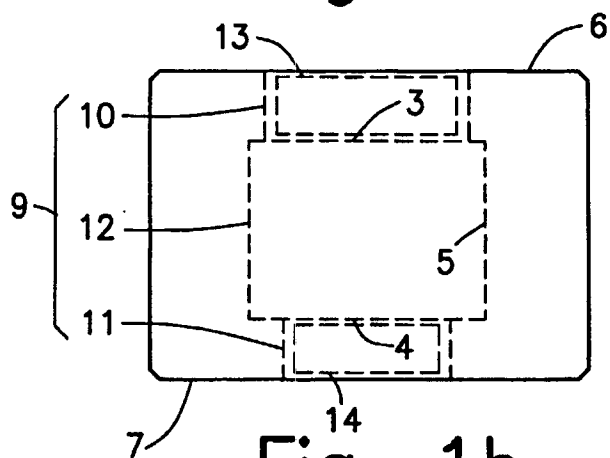


Fig. 1b

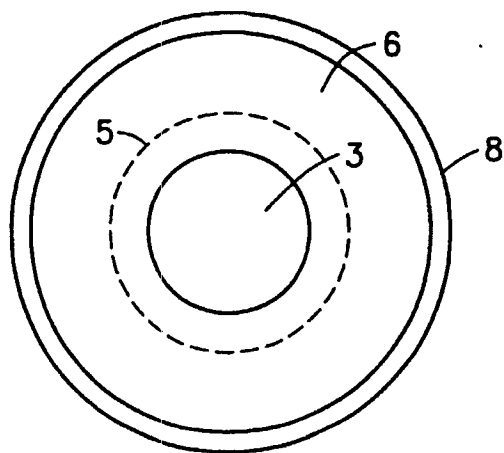


Fig. 1c

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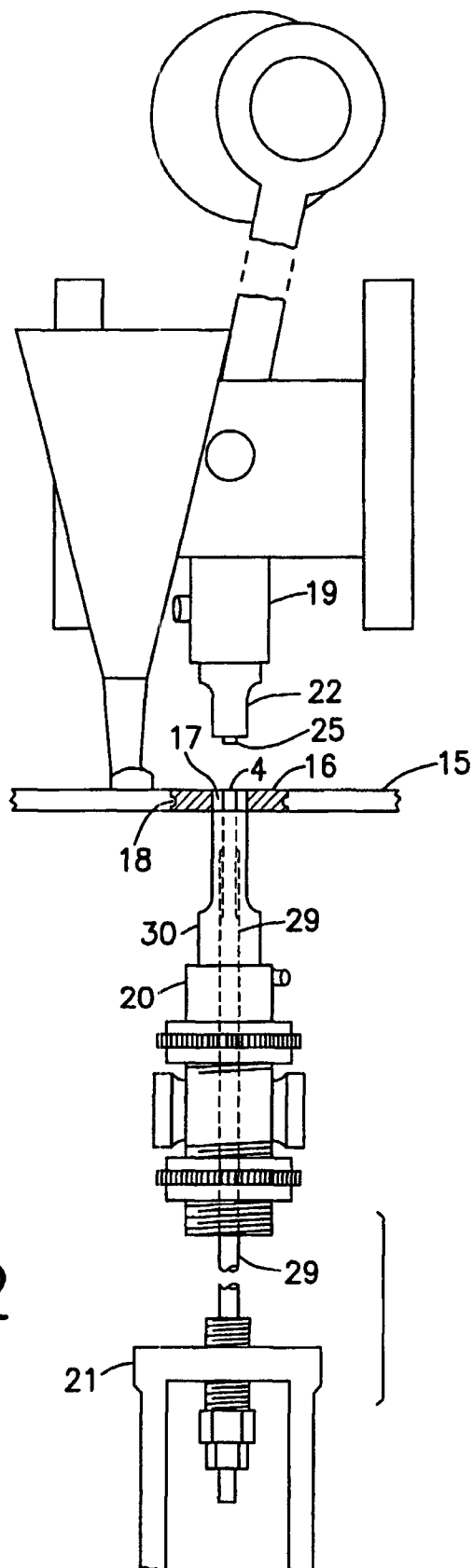


Fig. 2

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Fig. 3b

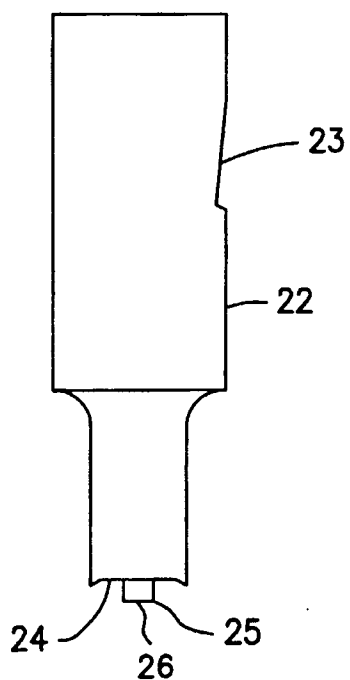
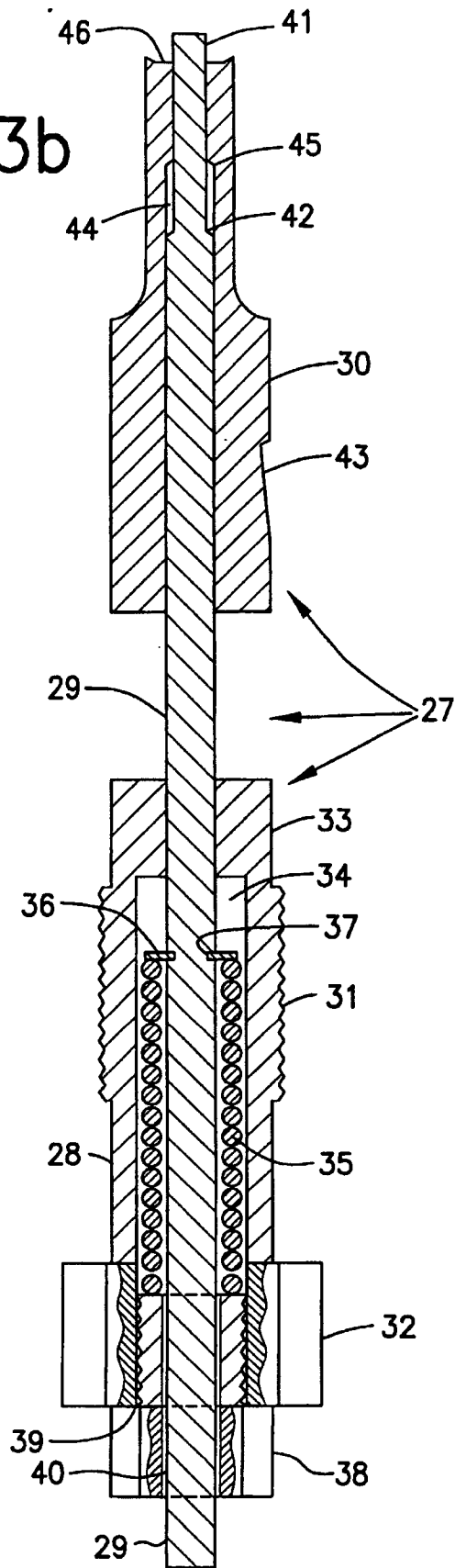


Fig. 3a



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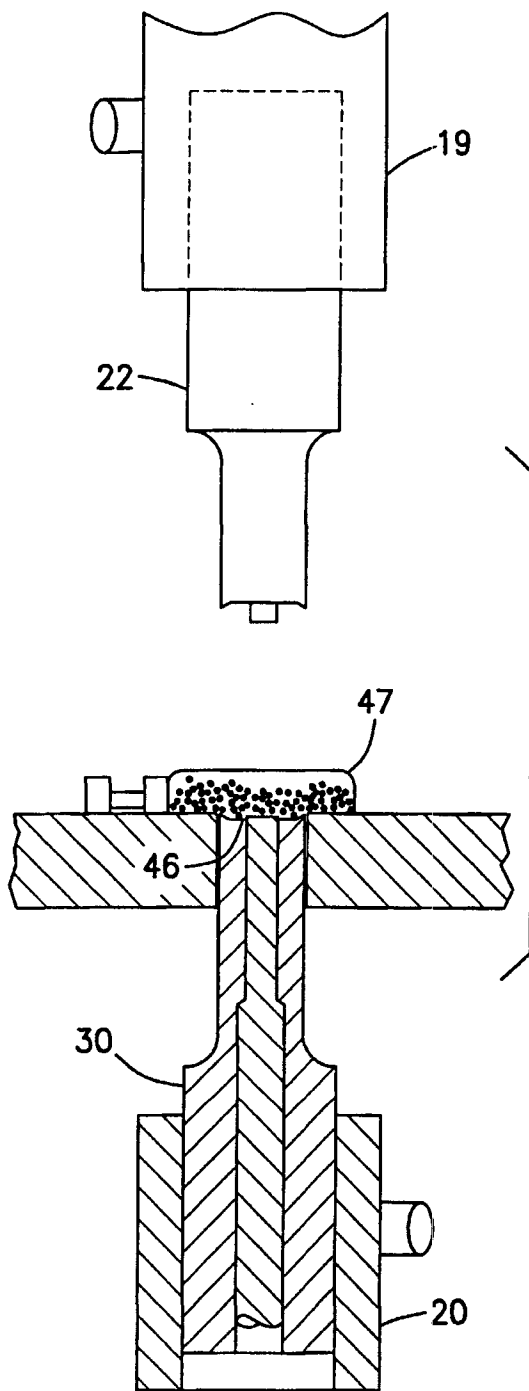


Fig. 4a

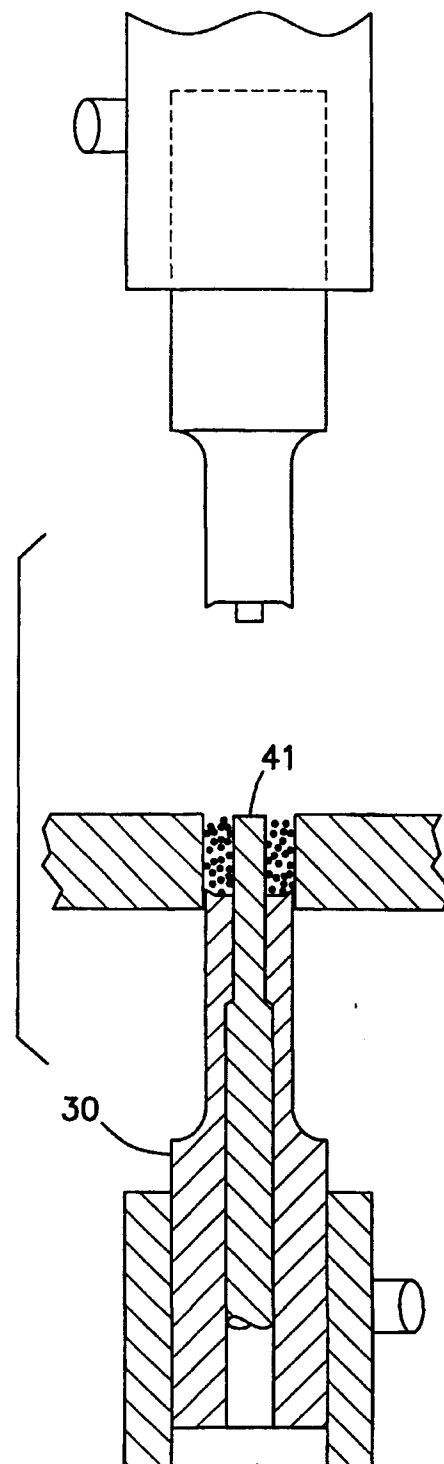


Fig. 4b

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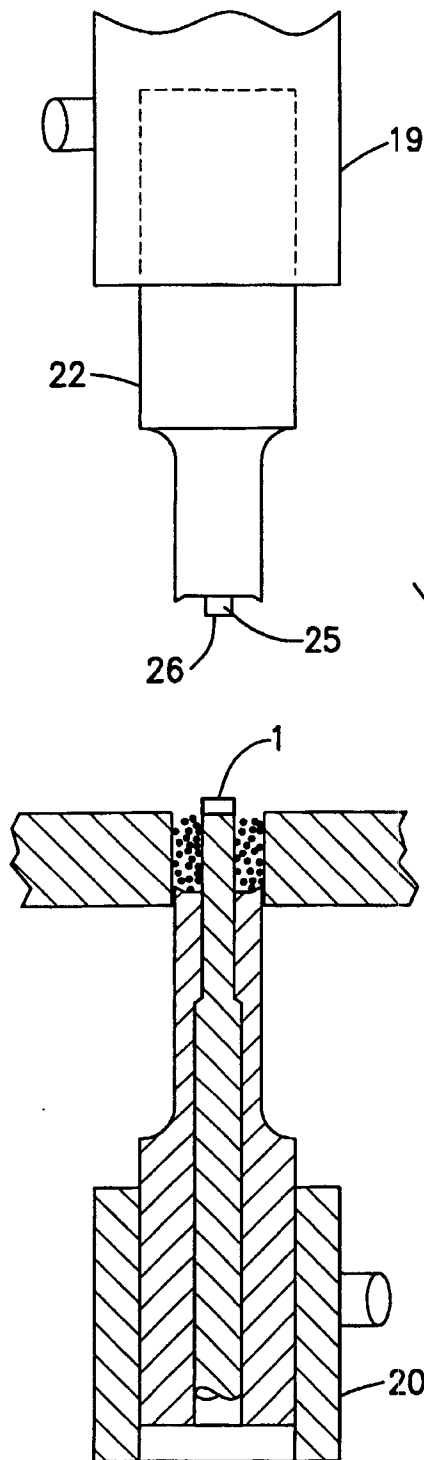


Fig. 4c

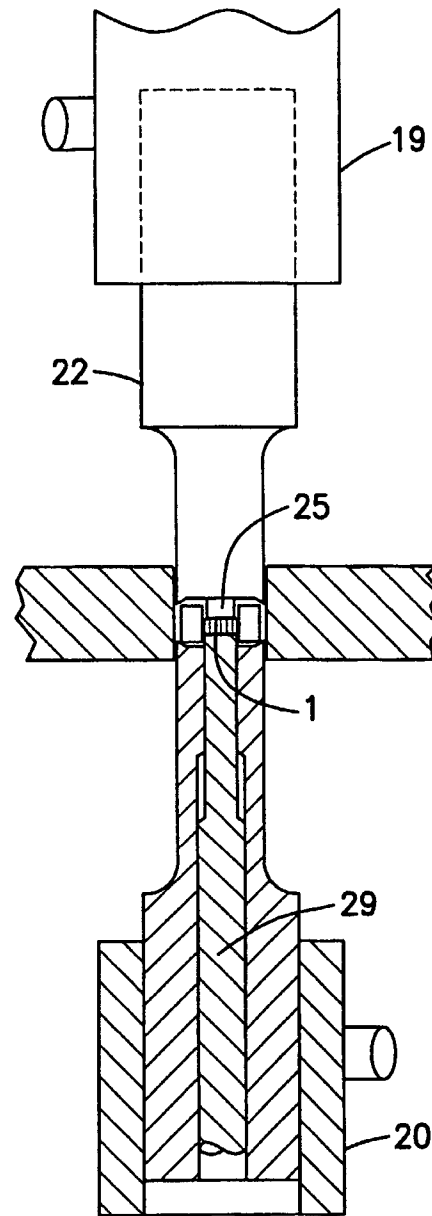


Fig. 4d

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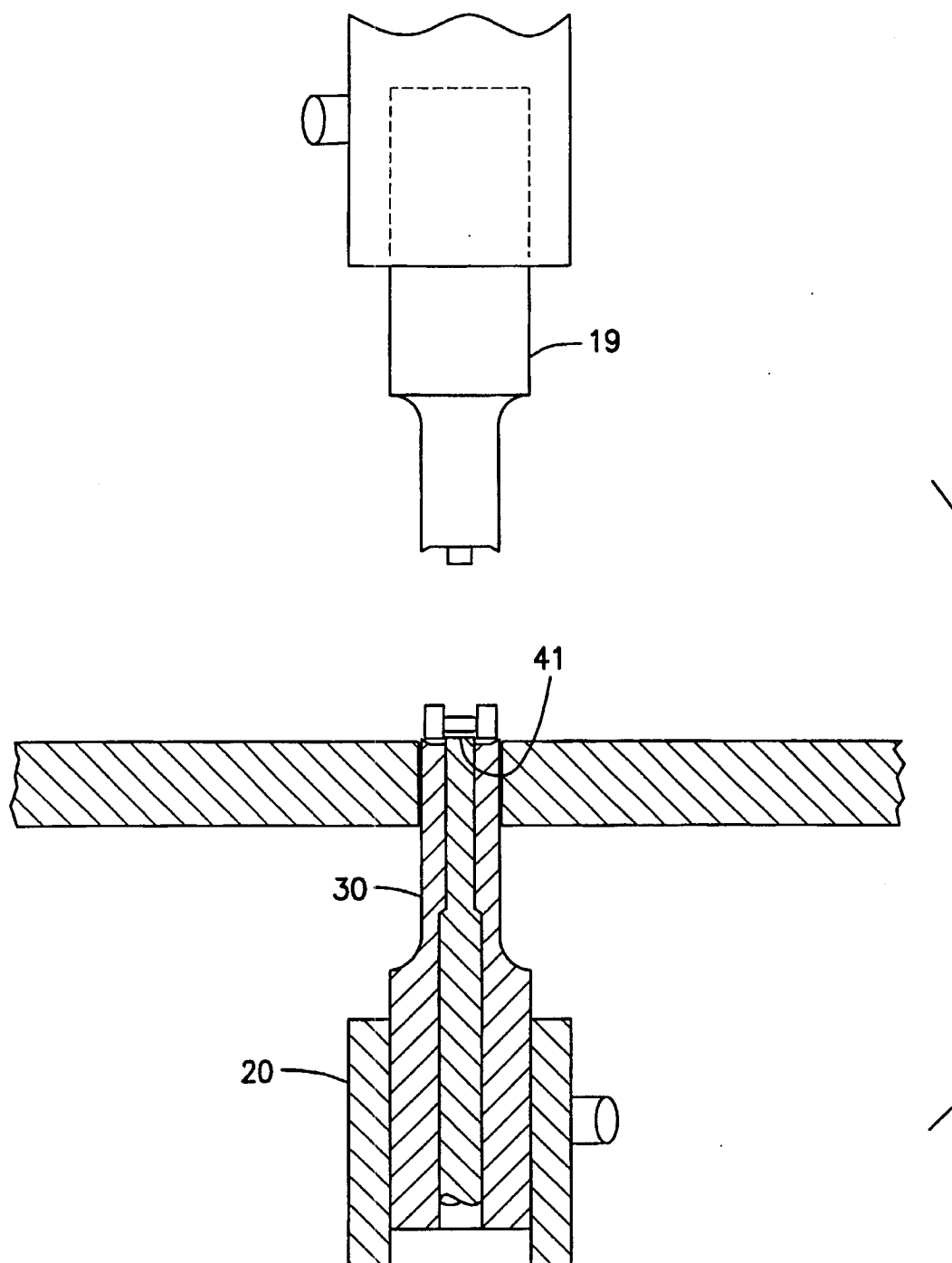


Fig. 4e

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Average Rate of Excretion of Alendronate by Twelve Human Subjects After Taking a 70 mg Dose in a Protected Tablet of The Invention and in a Prior Art Tablet

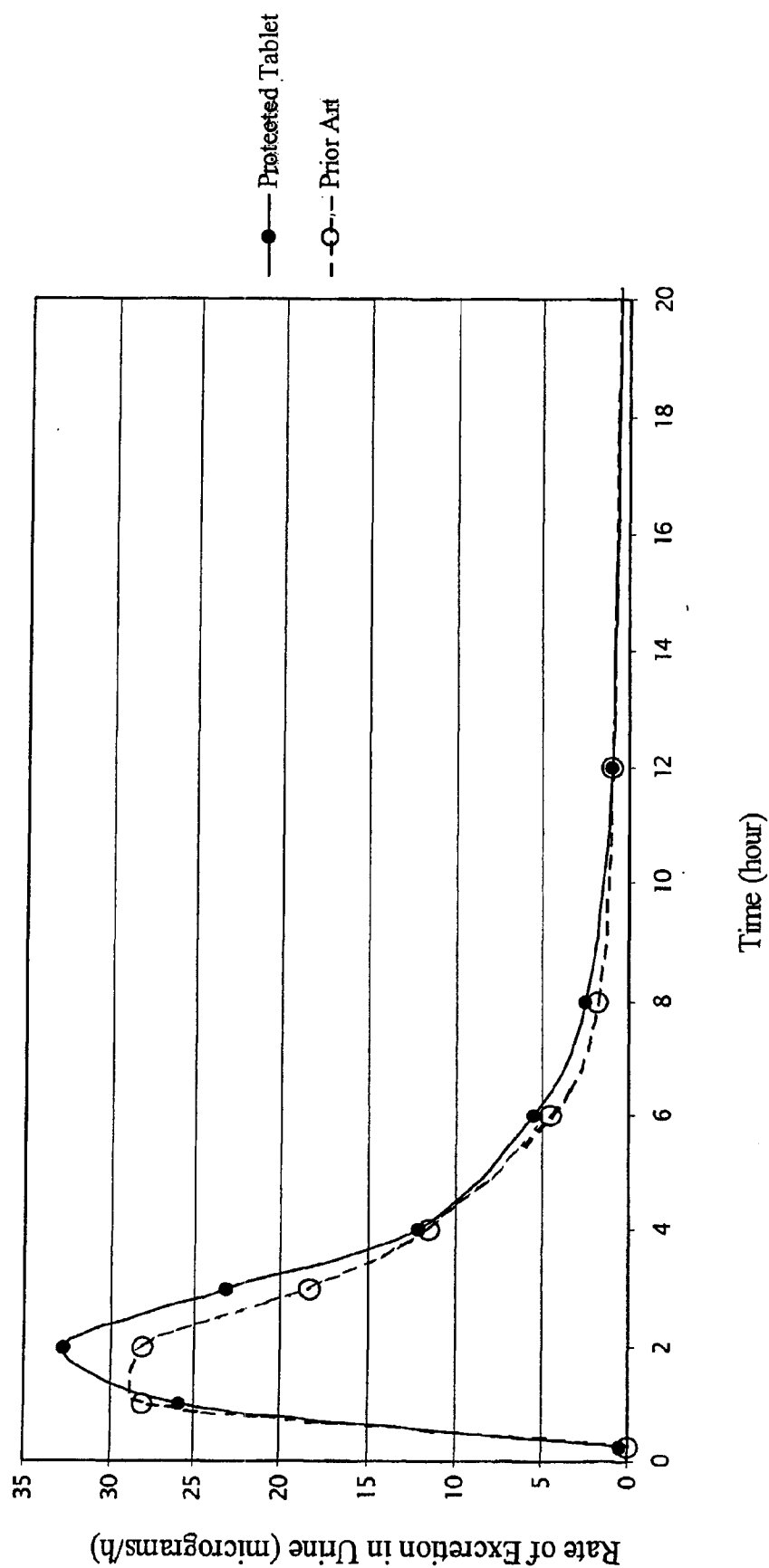


FIG. 5

EXHIBIT B

212



James Galbraith
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New York, NY 10004-1050
212.425.7200
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August 22, 2003

VIA FACSIMILE

Nicolas G. Barzoukas, Esq.
Howrey Simon Arnold & White
750 Bering Drive
Houston, TX 77057

Re: *Merck v. Teva (70 mg)*

Dear Nick:

We have reviewed your letter of yesterday with respect to International Patent Publication Number WO 03/057136. If Merck simply desires to "add this document to the record," then Teva will not oppose a motion to do so. By not opposing, Teva does not concede (1) that the document is relevant, (2) that it was responsive to any not-objected-to discovery requests, or (3) that Merck's request is timely.

If Merck intends to file a motion that includes any substantive characterization of the document, then Teva will oppose it. An example of the text of a motion that Teva would not oppose is:

Merck hereby moves to add International Patent Publication Number WO 03/057136 to the record in this case as PTX____. Counsel for Teva has stated that Teva does not oppose the motion.

Please call me if you want to discuss this issue further.

Very truly yours,

A handwritten signature in black ink, appearing to read 'James Galbraith'. Below the signature, the name 'James Galbraith' is printed in a standard font.

CERTIFICATE OF SERVICE

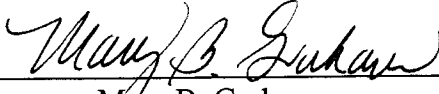
The undersigned hereby certifies that true and correct copies of the foregoing were caused to be served on August 22, 2003 upon the following counsel of record:

VIA HAND DELIVERY

Josy Ingersoll, Esq.
Adam Poff, Esq.
Young Conaway Stargatt & Taylor, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

VIA FEDERAL EXPRESS

James Galbraith, Esq.
Kenyon & Kenyon
One Broadway
New York, NY 10004



Mary B. Graham

EXHIBIT M

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,)	
)	
Plaintiff,)	
v.)	C.A. No. 04-939 (JJF)
)	
TEVA PHARMACEUTICALS USA, INC.)	
)	
Defendant.)	
)	

**MERCK & CO., INC.'S FIRST SET OF REQUESTS FOR
PRODUCTION OF DOCUMENTS AND THINGS (NOS. 1-85.)
TO DEFENDANT TEVA PHARMACEUTICALS USA, INC.**

Pursuant to Rule 34 of the Federal Rules of Civil Procedure, Plaintiff Merck & Co., Inc. ("Merck") request that Defendant Teva Pharmaceuticals USA, Inc. produce for inspection and copying the following documents and things in its possession, custody, or control. The requested documents and things are to be made available for inspection, copying, and/or photographing at the offices of HOWREY SIMON ARNOLD & WHITE, LLP, 750 Bering Drive, Houston, Texas 77057, thirty (30) days after the service hereof, or at such other time and location as may be mutually agreed upon by the parties. Documents shall be produced as required by Rule 34.

DEFINITIONS

A. "Teva" shall mean Teva Pharmaceuticals USA, Inc., and shall include (a) any divisions, departments, parents, subsidiaries, other organizational or operational units, and agents of Teva Pharmaceuticals USA, Inc., including but not limited to Teva Pharmaceutical Industries Ltd.; (b) all predecessor or successor companies or corporations; (c) all companies, corporations, partnerships, associations, or other business entities which are or have been under

the common ownership or control, in any manner, of Teva Pharmaceuticals USA, Inc.. and (d) each of the present and former officers, directors, employees, agents, attorneys, or other representatives of any of them.

- B. The term "Plaintiff" shall mean Merck.
- C. The term "Defendant" shall mean Teva.
- D. The term "parties" shall mean plaintiff and defendant.
- E. The term "'329 patent" shall mean U.S. Patent No. 5,994,329.
- F. The term "'932 patent" shall mean U.S. Patent No. 6,432,932.
- G. The term "'443 patent" shall mean U.S. Patent No. 6,465,443.
- H. The "patents-in-suit" shall mean the '329 patent, the '932 patent, and the '443 patent.

I. The term "document" shall have the broadest meaning possible under the Federal Rules of Civil Procedure and shall include, but not be limited to, the original (or a copy when the original is not available), each non-identical copy (including those which are non-identical by reason of notations or markings, or by appearing in the files of a separate person), and any books, notebooks, pamphlets, periodicals, letters, reports, memoranda, handwritten notes, notations, messages, telegrams, wires, cables, press or newswire releases, records, studies, analyses, summaries, magazines, booklets, circulars, labels, catalogs, bulletins, instructions, operating or maintenance manuals, operating or product specifications, fabrication sheets, laboratory notebooks, calendars, day timers, notes or records of meetings, notices, purchase orders, bills, ledgers, checks, tabulations, questionnaires, surveys, drawings, sketches, schematics, blueprints, flow sheets, working papers, charts, graphs, indices, tapes, agreements, releases, appraisals, valuations, estimates, opinions, financial statements, accounting records,

income statements, photographs, films or videotapes, tapes, minutes, contracts, leases, invoices, records of purchase or sale, correspondence, electronic or other transcription or taping of notes pertaining to telephone or personal conversations or conferences, tape recordings, electromagnetic recordings, digital recordings, voice mail messages and transcriptions thereof, interoffice and intraoffice communications of all types e-mail messages including printouts thereof, microfilms, CD-ROMs, videotapes or cassettes, films, movies computer printouts and all other written, printed, typed, punched, engraved, taped, filmed, recorded (electronically or otherwise), labeled, or graphic matter or thing, of whatever description, however produced or reproduced (including computer-stored or generated data), and shall include all attachments to (including tangible things) and enclosures with (including tangible things) any requested item, to which they are attached or with which they are enclosed, and each draft thereof.

J. The term “thing” shall mean any tangible object, other than a document, and includes objects of every kind and nature including, but not limited to, prototypes, models, samples and specimens.

K. The term “person” or “persons” shall mean an individual, corporation, proprietorship, partnership, association, joint venture, or any other entity.

L. The term “identify” (with respect to persons) shall mean to give, to the extent known, the person’s full name, present or last known address, and when referring to a natural person, additionally, the present or last known place of employment. Once a person has been identified in accordance with this subparagraph, only the name of that person need be listed in response to subsequent discovery requesting the identification of that person.

M. The term “identify” (with respect to documents) shall mean to give, to the extent known, the (i) type of document; (ii) general subject matter; (iii) date of the document; and (iv) author(s), addressee(s) and recipients(s).

N. “FDA” shall mean the United States Food and Drug Administration.

O. The term “Abbreviated New Drug Application” shall mean an Abbreviated New Drug Application filed with the FDA.

P. For purposes of Merck’s discovery requests only, the term “risedronate” refers to the compound 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid, as well as any pharmaceutical product or formulation containing this compound, including salts and esters thereof.

Q. The term “P&G” shall mean collectively The Procter & Gamble Company and/or Procter & Gamble Pharmaceuticals, and shall include (a) any divisions, departments, parents, subsidiaries, other organizational or operational units, and agents of The Procter & Gamble Company and/or Procter & Gamble Pharmaceuticals; (b) all predecessor or successor companies or corporations; (c) all companies, corporations, partnerships, associations, or other business entities which are or have been under the common ownership or control, in any manner, of The Procter & Gamble Company and/or Procter & Gamble Pharmaceuticals. and (d) each of the present and former officers, directors, employees, agents, attorneys, or other representatives of any of them.

R. The term “Teva’s Notice of Patent Certification” shall mean the letter regarding Teva’s Abbreviated New Drug Application No. 77-132 from Deborah Jaskot dated July 2, 2004 to the President or Counsel of Merck.

S. For purposes of these requests, terms not specifically defined shall be given their ordinary meaning. Should Defendant be unable to understand the meaning of any term, Defendant is invited to immediately seek clarification through Merck's counsel.

INSTRUCTIONS

A. These requests require Teva to produce all documents and things that are in Teva's actual or constructive possession, custody, or control or in the possession, custody or control of Teva's attorneys, accountants, representatives, consultants, agents, employees, or anyone else acting on Teva's behalf.

B. In the event Defendant claims that a request is overly broad, Defendant is requested to respond to that portion of the request that is unobjectionable and specifically identify the respect in which the request is allegedly overly broad.

C. In the event Defendant claims that a request is unduly burdensome, Defendant is requested to respond to that portion of the request that is unobjectionable and specifically identify the respect in which the request is allegedly unduly burdensome.

D. With respect to any document or thing that Defendant is unwilling to produce for inspection by Merck's counsel because the document or thing is asserted to be immune from discovery under the attorney-client privilege or work-product immunity, state separately with respect to each such document or thing sufficient information to disclose:

1. the general nature of each such document and/or thing, i.e., whether it is a letter, memorandum, report, pamphlet, etc.;
2. the date on which each such document and/or thing was reproduced or transcribed;

3. the name and business address of the person who signed or prepared each such document and/or thing or both and the name and business address of each such person who has edited, corrected, revised, or amended the same;

4. the name and business address of each person to whom any such document or thing was given or sent, or otherwise known to Defendant as being an intended or actual recipient of a copy thereof;

5. the name and address of the person having possession, custody, or control of each such document or tangible thing;

6. a brief indication of the subject matter of each such document or thing; and

7. the grounds for the claimed privilege or immunity as to each such document or thing.

E. These requests shall include documents and things created, acquired, or identified up to the date(s) of production and shall be deemed to be continuing. Therefore, Defendant shall promptly produce to Merck, as supplemental responses to these requests in accordance with Fed. R. Civ. P. 26(e), any additional documents or things that Defendant identifies, acquires, or becomes aware of up to and including the time of trial.

F. For any requested document that has been destroyed after August 13, 2004, Defendant shall identify each document, set forth the contents of each destroyed document, the date of such destruction, the identity of any individuals who authorized the destruction, and other circumstances related to such destruction.

REQUESTS FOR PRODUCTION

DOCUMENT REQUEST NO. 1

All documents and things that constitute, refer, or relate to the patents-in-suit.

DOCUMENT REQUEST NO. 2

All opinions, legal or otherwise, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other defense.

DOCUMENT REQUEST NO. 3

All documents and things, including correspondence and communications with counsel, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendant for any of the patents-in-suit or any other defense.

DOCUMENT REQUEST NO. 4

All documents and things relating to patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of the patents-in-suit.

DOCUMENT REQUEST NO. 5

All documents and things relating to any policies or practices of Defendant concerning patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendant of the patents of others.

DOCUMENT REQUEST NO. 6

Abbreviated New Drug Application No. 77-132, including all amendments and supplements thereto.

DOCUMENT REQUEST NO. 7

All Abbreviated New Drug Applications, including all amendments and supplements thereto, filed by Defendant with the FDA for risedronate.

DOCUMENT REQUEST NO. 8

All pharmaceutical applications, including all amendments and supplements thereto, relating to risedronate filed by Defendant with any regulatory agency, either in the United States or a foreign country.

DOCUMENT REQUEST NO. 9

All documents and things relating to or constituting correspondence or other communications, including but not limited to draft documents and correspondence, among Defendant¹ and/or between Defendant and/or any other person and any foreign or domestic regulatory agency, including but not limited to the FDA or a foreign counterpart to the FDA concerning risedronate.

DOCUMENT REQUEST NO. 10

All documents and things relating to the patent certifications made by Defendant as part of an Abbreviated New Drug Application for risedronate.

¹ Although the word “Defendant” is singular, the defined term “Defendant” includes all of the persons listed in the Merck’s definition of “Teva.”

DOCUMENT REQUEST NO. 11

All documents and things relating to the timing, schedule, timetable or projection of approval of Defendant's Abbreviated New Drug Application for risedronate.

DOCUMENT REQUEST NO. 12

All documents and things related to Teva's Notice of Patent Certification.

DOCUMENT REQUEST NO. 13

All documents and things relating to Defendant's decision to file a paragraph IV² patent certification as part of an Abbreviated New Drug Application for risedronate.

DOCUMENT REQUEST NO. 14

All documents and things relating to the first awareness of the patents-in-suit by Defendant.

DOCUMENT REQUEST NO. 15

All documents and things created before the filing of this suit concerning or constituting any search for publications and documents relating to any of the patents-in-suit.

DOCUMENT REQUEST NO. 16

All documents and things that Defendant contends support an allegation that any claim of any of the patents-in-suit is invalid.

² The term "paragraph IV" refers to 21 U.S.C. § 505(j)(2)(A)(vii)(IV)

DOCUMENT REQUEST NO. 17

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is not, and/or will not be, infringed by Defendant.

DOCUMENT REQUEST NO. 18

All documents and things forming the basis of, or relating to, any and all defenses pleaded by Defendant that any claim of the patents-in-suit is invalid.

DOCUMENT REQUEST NO. 19

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is invalid as lacking a written description.

DOCUMENT REQUEST NO. 20

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is invalid as the specification does not enable the claims.

DOCUMENT REQUEST NO. 21

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is invalid as indefinite.

DOCUMENT REQUEST NO. 22

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is invalid as lacking utility.

DOCUMENT REQUEST NO. 23

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is anticipated.

DOCUMENT REQUEST NO. 24

All documents and things forming the basis of, or relating to, Defendant's contention that any of the claims of the patents-in-suit is invalid as obvious.

DOCUMENT REQUEST NO. 25

All documents and things relating to any legal or administrative proceedings concerning the manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of risedronate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 26

All documents and things concerning any indemnification provided to or received by, or granted by Defendant against or for the infringement of any of the patents-in-suit.

DOCUMENT REQUEST NO. 27

All documents and things concerning any insurance provided to or received by, or granted by Defendant against or for the infringement of any of the patents-in-suit.

DOCUMENT REQUEST NO. 28

All documents and things relating to U.S. or foreign lawsuits, investigations, or administrative proceedings regarding Defendant's production of risedronate.

DOCUMENT REQUEST NO. 29

All documents and things relating to any manufacture, importation, use, sale, and/or offer for sale of pharmaceutical formulations of risedronate in the U.S. by Defendant or any other person.

DOCUMENT REQUEST NO. 30

All documents and things relating to any supply agreement for risedronate.

DOCUMENT REQUEST NO. 31

All documents and things relating to any desire, consideration or need by Defendant to obtain or not obtain a license under any of the patents-in-suit.

DOCUMENT REQUEST NO. 32

All documents and things related to licensing agreements among Defendant and/or between Defendant and any other person for the production, distribution or sale of risedronate.

DOCUMENT REQUEST NO. 33

All documents and things relating to any potential labeling, promotion, advertising or claims to be used in marketing risedronate by Defendant in the U.S or any other country.

DOCUMENT REQUEST NO. 34

All documents and things concerning marketing or whether to market risedronate in the U.S. or any other country.

DOCUMENT REQUEST NO. 35

All documents and things relating to market share and market potential for risedronate in the U.S. or any other country.

DOCUMENT REQUEST NO. 36

All documents and things relating to the dollar amounts expended or predicted to be expended by Defendant or any other person for the promotion of risedronate in the U.S. or any other country.

DOCUMENT REQUEST NO. 37

All documents and things relating to any comparison of risedronate to any other product.

DOCUMENT REQUEST NO. 38

All documents and things relating to any comparison of risedronate to any product containing a bisphosphonate (including salts and esters thereof).

DOCUMENT REQUEST NO. 39

All documents and things relating to the dollar amounts expended by Defendant or any other person for the preparation and filing of Abbreviated New Drug Application No. 77-132.

DOCUMENT REQUEST NO. 40

All documents and things relating to all forms of promotions for or marketing of risedronate in the U.S. or any other country by Defendant or any other person.

DOCUMENT REQUEST NO. 41

All documents and things relating to any communications to or from Defendant's sales force, agents, dealers, representatives, distributors, the press, or any news wire service relating to this lawsuit, and/or any of the patents-in-suit.

DOCUMENT REQUEST NO. 42

All documents and things relating to any market survey, market analysis, sales projections or forecast of customer demand with respect to risedronate in the U.S. or any other country.

DOCUMENT REQUEST NO. 43

All documents and things relating to Defendant's research and development efforts related to risedronate.

DOCUMENT REQUEST NO. 44

All documents and things relating to Defendant's research and development of tablets containing risedronate.

DOCUMENT REQUEST NO. 45

All documents and things relating to patent applications, including the patents themselves, filed in any country by Defendant referencing, referring, or relating to risedronate.

DOCUMENT REQUEST NO. 46

All documents and things relating to any tests comparing P&G's risedronate product with the risedronate product that Defendant or any other person has produced.

DOCUMENT REQUEST NO. 47

Any samples of P&G products that contain risedronate that have been tested or examined by Defendant or any persons working on its behalf and the results of any such tests or examinations.

DOCUMENT REQUEST NO. 48

All documents and things relating to any testing performed using P&G's risedronate.

DOCUMENT REQUEST NO. 49

All documents and things relating to Defendant's knowledge of Merck's, P&G's, or any other entity's activities in the research, patenting, development, manufacture, marketing, use or sale of any pharmaceutical formulation of risedronate.

DOCUMENT REQUEST NO. 50

All documents and things relating to Defendant's activities in the research, patenting, development, manufacture, marketing, use or sale of any pharmaceutical formulation of risedronate or any other bisphosphonate, including salts and esters thereof.

DOCUMENT REQUEST NO. 51

All documents and things Defendant contemplates introducing at trial.

DOCUMENT REQUEST NO. 52

All documents and things relied upon or referred to in preparing the Answer to Merck's Complaint in this action and Teva's Notice of Patent Certification, including, but not limited to, all reports, analyses, test results, or other materials.

DOCUMENT REQUEST NO. 53

All documents and things produced to any other parties in connection with discovery in U.S. and foreign litigations concerning, referring, or relating to risedronate.

DOCUMENT REQUEST NO. 54

All documents and things relating to any experts Defendant contemplates calling at trial, including but not limited to the educational and technical training of each expert and any publications authored by such expert.

DOCUMENT REQUEST NO. 55

All documents and things, including but not limited to organizational charts, showing identity and job titles of employees for all of Defendant's divisions and/or subsidiaries involved in the research, development, production, analysis, design, manufacture, sale, distribution, marketing, or market analysis of risedronate.

DOCUMENT REQUEST NO. 56

All documents and things setting forth Defendant's document retention and/or destruction policies.

DOCUMENT REQUEST NO. 57

All documents and things relating to or constituting applications by Defendant to obtain regulatory approval for risedronate in a foreign country.

DOCUMENT REQUEST NO. 58

All documents and things referring or relating to correspondence between Defendant and P&G referring or relating to risedronate.

DOCUMENT REQUEST NO. 59

All documents and things referring or relating to correspondence between Defendant and any third party relating to risedronate.

DOCUMENT REQUEST NO. 60

All documents and things that Defendant has submitted to or received from the FDA referring or relating to risedronate.

DOCUMENT REQUEST NO. 61

All documents and things referring or relating to safety and efficacy testing of risedronate.

DOCUMENT REQUEST NO. 62

All documents and things from the files of Deborah Jaskot referring or relating to risedronate.

DOCUMENT REQUEST NO. 63

All documents and things reflecting meeting minutes or notes or records of any meeting referring or relating to risedronate.

DOCUMENT REQUEST NO. 64

All documents and things reflecting correspondence referring to or relating to meeting minutes or notes or records of any meeting referring or relating to risedronate.

DOCUMENT REQUEST NO. 65

All documents and things reflecting meeting minutes or notes or records of any meeting referring or relating to osteoporosis or drugs used in the treatment or prevention of osteoporosis.

DOCUMENT REQUEST NO. 66

All documents and things in the possession, custody or control of Deborah Jaskot referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 67

All documents and things from the files of Marc Goshko referring or relating to risedronate.

DOCUMENT REQUEST NO. 68

All documents and things in the possession, custody or control of Marc Goshko referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 69

All documents and things from the files of Christopher Pelloni referring or relating to risedronate.

DOCUMENT REQUEST NO. 70

All documents and things in the possession, custody or control of Christopher Pelloni referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 71

All documents and things from the files of William Marth referring or relating to risedronate.

DOCUMENT REQUEST NO. 72

All documents and things in the possession, custody or control of William Marth referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 73

All documents and things from the files of Uzi Karniel referring or relating to risedronate.

DOCUMENT REQUEST NO. 74

All documents and things in the possession, custody or control of Uzi Karniel referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 75

All documents and things from the files of Kenyon & Kenyon referring or relating to risedronate.

DOCUMENT REQUEST NO. 76

All documents and things in the possession, custody or control of Kenyon & Kenyon referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 77

All documents and things from the files of William A. Fletcher referring or relating to risedronate.

DOCUMENT REQUEST NO. 78

All documents and things in the possession, custody or control of William A. Fletcher referring or relating to osteoporosis or to any drug used in the treatment and prevention of osteoporosis.

DOCUMENT REQUEST NO. 79

All documents and things received from any individuals or organizations related to risedronate.

DOCUMENT REQUEST NO. 80

All documents and things relating or referring to prescription volume or prescription data for risedronate.

DOCUMENT REQUEST NO. 81

All documents and things relating or referring to market share or sales of risedronate.

DOCUMENT REQUEST NO. 82

All documents and things referring or relating to any bisphosphonate, including salts and esters thereof.

DOCUMENT REQUEST NO. 83

All documents and things referring or relating to any consideration by Defendant for filing an Abbreviated New Drug Application for any bisphosphonate, including salts and esters thereof.

DOCUMENT REQUEST NO. 84

All documents and things referring or relating to the license between Merck and P&G for risedronate products.

DOCUMENT REQUEST NO. 85

One hundred of each of the different tablet doses covered by Teva's Abbreviated New Drug Application No. 77-132.


OF COUNSEL:

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April 25, 2005
462087

MORRIS, NICHOLS, ARSHT & TUNNELL


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Attorneys for Plaintiff Merck & Co., Inc.

CERTIFICATE OF SERVICE

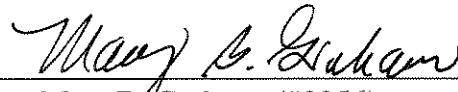
I hereby certify that on the 25th day of April, 2005, true and correct copies of the foregoing were caused to be served upon the following individuals in the manner indicated:

BY HAND

Josy Ingersoll, Esquire
YOUNG CONAWAY STARGATT
& TAYLOR, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

BY FEDERAL EXPRESS

James Galbraith, Esquire
KENYON & KENYON
One Broadway
New York, NY 10004



Mary B. Graham (#2256)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Merck & Co., Inc.

DEFENDANTS

Teva Pharmaceuticals USA, Inc.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF
(EXCEPT IN U.S. PLAINTIFF CASES)

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM ADDRESS AND TELEPHONE NUMBER)

Mary B. Graham
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street; PO Box 1347
Wilmington, DE 19899-1347
302-658-9200

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
☐ 2 U.S. Government Defendant
☒ 3 Federal Question (U.S. Government Not a Party)
☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

- | | | | | | |
|---|----------------------------|----------------------------|---|----------------------------|----------------------------|
| | PTF | DEF | | PTF | DEF |
| Citizen of This State | <input type="checkbox"/> 1 | <input type="checkbox"/> 1 | Incorporated or Principal Place of Business in This State | <input type="checkbox"/> 4 | <input type="checkbox"/> 4 |
| Citizen of Another State | <input type="checkbox"/> 2 | <input type="checkbox"/> 2 | Incorporated and Principal Place of Business in Another State | <input type="checkbox"/> 5 | <input type="checkbox"/> 5 |
| Citizen or Subject of a Foreign Country | <input type="checkbox"/> 3 | <input type="checkbox"/> 3 | Foreign Nation | <input type="checkbox"/> 6 | <input type="checkbox"/> 6 |

IV. NATURE OF SUIT (PLACE AN "X" IN ONE BOX ONLY)

CONTRACT	TORTS	FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
<input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgement <input type="checkbox"/> 151 Medicare Act <input type="checkbox"/> 152 Recovery of Defaulted Student Loans (Excl Veterans) <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholder Suits <input type="checkbox"/> 190 Other Contract <input type="checkbox"/> 195 Contract Product Liability	PERSONAL INJURY <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault Libel & Slander <input type="checkbox"/> 330 Federal Employers Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury	PERSONAL INJURY <input type="checkbox"/> 362 Personal Injury - Med Malpractice <input type="checkbox"/> 365 Personal Injury - Product Liability <input type="checkbox"/> 368 Asbestos Personal Injury Product Liability PERSONAL PROPERTY <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage Product Liability	<input type="checkbox"/> 610 Agriculture <input type="checkbox"/> 620 Other Food & Drug <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 630 Liquor Laws <input type="checkbox"/> 640 R R & Truck <input type="checkbox"/> 650 Airline Regs <input type="checkbox"/> 660 Occupational Safety/Health <input type="checkbox"/> 690 Other	<input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157 PROPERTY RIGHTS <input type="checkbox"/> 820 Copyrights <input checked="" type="checkbox"/> 830 Patent <input type="checkbox"/> 840 Trademark
REAL PROPERTY <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent Lease & Ejectment <input type="checkbox"/> 240 Torts to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property	CIVIL RIGHTS <input type="checkbox"/> 441 Voting <input type="checkbox"/> 442 Employment <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 444 Welfare <input type="checkbox"/> 440 Other Civil Rights	PRISONER PETITIONS <input type="checkbox"/> 510 Motions to Vacate Sentence HABEAS CORPUS: <input type="checkbox"/> 530 General <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus & Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Condition	LABOR <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 730 Labor Mgmt. Reporting & Disclosure Act <input type="checkbox"/> 740 Railway Labor Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl Ret Inc Security Act	<input type="checkbox"/> 861 HIA (1395ff) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g)) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g)) FEDERAL TAX SUITS <input type="checkbox"/> 870 Taxes (U.S. Plaintiff or Defendant) <input type="checkbox"/> 871 IRS - Third Party 26 USC 7609
				<input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 410 Antitrust <input type="checkbox"/> 430 Banks or Banking <input type="checkbox"/> 450 Commerce/ICC Rates/etc <input type="checkbox"/> 460 Deportation <input type="checkbox"/> 470 Racketeer Influenced and Corrupt Organizations <input type="checkbox"/> 810 Selective Service <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 875 Customer Challenge 12 USC 3410 <input type="checkbox"/> 891 Agricultural Acts <input type="checkbox"/> 892 Economic Stabilization Act <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 894 Energy Allocation Act <input type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 900 Appeal of Fee Determination Under Equal Access to Justice <input type="checkbox"/> 950 Constitutionality of State Statutes <input type="checkbox"/> 890 Other Statutory Actions

V. ORIGIN

(PLACE AN "X" IN ONE BOX ONLY)

- ☒ 1 Original Proceeding
☐ 2 Removed From State Court
☐ 3 Remanded From Appellate Court
☐ 4 Reinstated or Reopened
☐ 5 Transferred From another district (specify) _____
☐ 6 Multidistrict Litigation
☐ 7 Appeal to District Judge from Magistrate Judgement

VI. CAUSE OF ACTION

(CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE
DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY)

Patent infringement under 35 U.S.C. § 271 and independent action based on Fed. R. Civ. P. 60(b) to set aside judgment in C.A. No. 01-048 (JJF).

VII. REQUESTED IN COMPLAINT**DEMAND \$**

CHECK YES only if demanded in complaint:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

JURY DEMAND: ☐ YES ☒ NO**VIII. RELATED CASE(S) IF ANY** (See Instructions)

JUDGE Joseph J. Farnan, Jr.
Gregory M. Sleet

DOCKET NUMBER C.A. No. 01-048-JJF
C.A. No. 04-939-GMS
C.A. No. 05-658-GMS
C.A. No. 06-230-GMS

DATE

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

06 - 310

Civil Action No. _____

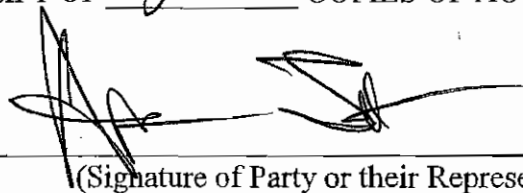
ACKNOWLEDGMENT
OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A
UNITED STATES MAGISTRATE JUDGE
TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 2 COPIES OF AO FORM 85.

5.10.06

(Date forms issued)


(Signature of Party or their Representative)

Aaron Samston

(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action